

# Exhibit A

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM  
POWDER PRODUCTS MARKETING, SALES  
PRACTICES AND PRODUCTS LIABILITY  
LITIGATION**

**MDL NO. 16-2738 (FLW) (LHG)**

***THIS DOCUMENT RELATES TO ALL CASES***

**EXPERT REPORT OF BROOKE TAYLOR MOSSMAN, MS, PHD  
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019



Brooke Taylor Mossman, M.S., Ph.D.

## **I. Scope Of Report**

I was asked to address whether there is scientific evidence to support the theory that nonasbestos cleavage fragments present health risks to humans and the biological plausibility of plaintiffs' theory that cosmetic talc particles can migrate to the ovaries and cause cancer. I was also asked to review the experiments of Dr. Saed and the lab notebooks that were submitted by plaintiffs' counsel on his behalf and to comment on the opinions of Dr. Zelikoff. All the opinions in this report are stated to a reasonable degree of scientific certainty. I am being compensated at my customary rate of \$550.00 per hour for my work related to this litigation.

## **II. Summary Of Opinions**

Cosmetic talc particles and nonasbestos cleavage fragments are different chemically, physically and structurally from the amphibole asbestos types, crocidolite and amosite.

Because of these different properties, cosmetic talc particles and nonasbestos cleavage fragments are unlikely to reach or be retained at sites of development of mesotheliomas or ovarian cancers.

Talc and nonasbestos cleavage fragments are not reactive with cells, and effective repair pathways occur. Because they are distinct in chemistry and other features from asbestos fibers, they do not have the potential to cause the abnormal cell responses that are integral to the development of cancers.

The trace amounts of cleavage fragments or other minerals that may be present in industrial or cosmetic talcs have little or no chemical or biological reactivity and do not play a role in critical cellular and molecular pathways leading to the development of mesotheliomas or ovarian cancers.

The results of numerous epidemiologic and experimental studies assessing the carcinogenic (cancer causing) potential of short asbestos fibers (<5-10 microns in length) support the concept that short fibers and cleavage fragments, even of respirable dimensions, do not play a role in the induction of tumors.

Experimental studies demonstrate no observed adverse effect levels from exposure to certain concentrations of asbestos fibers, indicating the existence of a threshold for cancer causation below which tumors do not occur.

Gene expression studies show that mesothelial cells exhibit dose- and time-related changes in response to tumor-causing asbestos fibers, but not in response to talc. Ovarian epithelial cells are more resistant to gene changes by asbestos fibers and do not show inflammatory or cancer-related gene expression in response to talc.

There is no scientifically plausible pathway of migration to the ovary or fallopian tubes by cosmetic talc particles, as would be required for talc to cause ovarian cancers.

Dr. Saed's research does not in any way support or advance the theory that perineal talc use can cause ovarian cancer. His experimental design, methods and data are deeply flawed, he appears to have little to no knowledge about the origins of ovarian cancers, and he makes false analogies and speculative leaps in his report. His failure to disclose the source of his research funding for talc studies and sloppy, altered research notebooks further suggest that he conducted this research to advance litigation and not to advance scientific knowledge.

Dr. Zelikoff's conclusions are not supported by peer-reviewed scientific papers in the literature or basic tenets of toxicology and carcinogenesis. She exhibits little understanding of the properties of talc or asbestos, and simply repeats other plaintiffs' experts' flawed theories of talc migration and inflammation. Portions of her report are copied from the Internet without citation or verbatim from other experts' reports, again without citation, highlighting the unscientific nature of her opinions. The lack of rigor in preparing her report and citations from legal documents would not be acceptable in the peer-reviewed scientific literature.

Each of my opinions is supported by my own research and scholarship in cancer research on asbestos for more than 40 years. I have organized and attended national and international scientific meetings on mechanisms of asbestos-related cancers and have served on key panels addressing cancer risks of minerals. I have also organized and participated in meetings between geologists and biologists seeking to understand the respective differences in minerals that might explain their different potencies in disease development. My opinions are also a product of my current review of the peer-reviewed scientific literature, editorial and reviewer activities, and participation on National Institutes of Health (NIH) study sections and scientific panels. I have had uninterrupted national research funding throughout my career. All of my research on asbestos fibers, talc and cleavage fragments has been published in peer-reviewed, high-impact scientific journals prior to the advent of my participation in talc litigation in 2014. In this report, I often reference reviews of my work and others in peer-reviewed papers and provide a glossary of scientific terms for clarification.

### **III. Background And Qualifications**

My M.S. degree at the University of Vermont in 1970 was granted in human physiology, where I studied diagnostic methods for the detection of cervical cancers in the Department of Obstetrics and Gynecology in the Medical School. After moving to New York University, where I worked as a research assistant studying mechanisms of skin cancer, I returned to obtain my Ph.D. in Cell Biology from the University of Vermont in 1977 on mechanisms of asbestos-induced cancers. I am currently a Professor Emeritus and University Distinguished Professor of Pathology at the University of Vermont College of Medicine. I have been studying the roles of asbestos fibers in the induction of lung cancers, asbestosis, and mesotheliomas in the Department of Pathology at the University of Vermont College of Medicine for more than 40 years. Through research grant awards by several institutes of the NIH, Environmental Protection Agency (EPA) and American Cancer Society awarded to me throughout my career, I have elucidated the importance of inflammation-causing, genetic and cell signaling pathways by amphibole asbestos (with an emphasis on crocidolite) in the causation of lung cancers and mesotheliomas. Recent research



has focused on blocking these pathways in experimental studies to allow the development of therapeutic approaches for patients with mesothelioma. I have performed inhalation studies in rodents, studied the effects of asbestos types and other minerals (serpentine and amphibole cleavage fragments of asbestos, talc, etc.) on rodent and human ovarian epithelial and mesothelial cells, i.e., *in vitro* studies, and confirmed many of these observations in both human mesothelioma tissues and a model of peritoneal mesothelioma after injection of human mesothelioma cells into immunocompromised mice.

My fields of specialization include: environmental toxicology, mesothelial and epithelial cell differentiation, chemical and physical carcinogenesis and cell injury, pulmonary fibrosis, reactive oxygen species (ROS), molecular biology of antioxidant enzymes, and cell signaling pathways leading to inflammation and cancer. My scholarship has included a focus on asbestos-induced diseases, and I have made numerous and sustained contributions to the field of fiber carcinogenesis and the study of asbestos. My work serves as a foundation for significant amounts of research on asbestos-related diseases.

I have published more than 300 refereed papers, books, book chapters, reviews and monographs on my research in the scientific literature and have chaired and presented my research at more than 100 meetings and seminars on mechanisms of asbestos- and silica-related diseases. I have received numerous national and international meeting invitations to present my research, as well as awards for my research accomplishments that include the prestigious Wagner Award for historic contributions to mesothelioma research from the International Mesothelioma Interest Group, a Career Achievement Recognition Award for Scientific Accomplishments from the American Thoracic Society, appointment to the Board of Councilors of the National Cancer Institute, and election to the Plutocrat Society of the University Associates in Pathology.

At the University of Vermont, I have directed an Environmental Pathology training grant from the National Institute of Environmental Health Sciences (NIEHS) (1995-2013), have served as Director of the University's Environmental Pathology Program (1995-2013), and am a former Chair of the Cell and Molecular Biology Program (1984-88). In 2011, I received one of only 10 University Distinguished Professor Awards, awarded historically in recognition of outstanding contributions to my discipline. The award noted that my "scientific contributions over the past 30 years are numerous and sustained, resulting in international recognition as one of the world's foremost authorities in the field of fiber carcinogenesis." This is a lifetime award that allows me to maintain my University office and service activities. I have also won both Medical Scholar and Alumni Achievement Awards for "outstanding achievements in research, education, public service and humanitarianism" in the UVM College of Medicine, and I have recently been elected to the Vermont Academy of Arts and Sciences "as a leading researcher in asbestos-induced carcinogenesis."

I have served on numerous advisory boards at other universities as well as scientific advisory boards and study sections of the National Heart, Lung and Blood Institute (NHLBI), National Cancer Institute (NCI), American Cancer Society, NIEHS, and EPA. I was the first woman to chair the advisory board of the Lung Institute of NHLBI and have most recently served as Chair of grant review panels for this institute and others. I have also organized and chaired

international and national conferences featuring experts in the fields of mineralogy, asbestos and mesothelioma research. Through review of research grants and papers as part of my editorial services for a number of scientific journals, I keep up with contemporary developments in my field of research.

I was a reviewer of both the EPA strategic plan for studies on Libby amphibole as well as the “NIOSH Roadmap for Research on Asbestos Fibers and Other Elongate Mineral Particles” on behalf of the Institute of Medicine National Academies. I served on the founding board of the Center for Asbestos-Related Diseases (CARD) in Libby, Montana, where I was awarded a Focus Award for my dedication and voluntary contributions, and have just completed a voluntary term on the scientific advisory board of the Mesothelioma Applied Research Foundation (MARF). I am currently serving on the scientific review committee for the National Virtual Mesothelioma Bank, and am on the external advisory board for an NIH-funded Superfund grant on asbestos at the University of Pennsylvania. I have been invited recently to serve on the International Mineralogical Association working group panel “[t]o clarify issues associated with asbestos and other respirable minerals-nomenclature and classification” and was one of six invited speakers and session coordinators at a conference on “Asbestos in Talc” in November 2018 at The Joint Institute of Food Safety and Applied Nutrition (FDA). I am, or have been, a member of the American Society of Cell Biology, American Association for the Advancement of Science, Sigma Xi Scientific Honor Society, Oxygen Society, Tissue Culture Association, American Association for Cancer Research, International Association for the Study of Lung Cancer, American Thoracic Society, and the American Society of Investigative Pathology. I serve on the editorial board or as a reviewer for: *Journal of Cellular Physiology*, *Environmental Research*, *Cell Biology & Toxicology*, *In Vitro Toxicology*, *Cancer Research*, *Experimental Cell Research*, *Experimental Lung Research*, *Scanning Electron Microscopy*, *American Journal of Pathology*, *Science*, *American Industrial Hygiene Association Journal*, *European Journal of Cancer & Clinical Oncology*, *Journal of Toxicology and Applied Pharmacology*, *Environmental Mutagenesis*, *Carcinogenesis*, *American Review of Respiratory Diseases*, *Journal of the American College of Toxicology*, *Journal of the National Cancer Institute*, *Nature*, *Journal of Leukocyte Biology*, *New England Journal of Medicine*, *Cell & Tissue Kinetics*, *Clinical Pathology and Pharmacology*, *American Journal of Respiratory Cell and Molecular Biology*, *Risk Analysis*, *Clays and Clay Minerals*, *Chest*, *Chemical Research in Toxicology*, *Atherosclerosis*, *Journal of Clinical and Laboratory Medicine*, *New Journal of Chemistry*, *Drug and Chemical Toxicology* (past section Head of In Vitro Toxicology), *Particle and Fibre Toxicology*, *PLOS*, *Cancer Letters*, *Oncotarget*, and *Archives of Biochemistry & Biophysics*.

My roles as an editor and reviewer of many scientific journals for decades have made me aware of the importance of disclosures and rigor in reviewing that were ignored in submissions of Dr. Saed’s recent abstracts and paper.

These many tasks have also led to formulation of my scientific opinions as outlined above.

My prior deposition and trial testimony for the last four years is listed in **Exhibit A**, references cited within my report, including those supporting my opinions, are listed in **Exhibit B**, and a copy of my complete *Curriculum Vitae* is attached as **Exhibit C**.

#### IV. Scientific Methodology And The Importance Of The Scientific Peer Review Process

Publishing one's research findings in the peer-reviewed scientific literature is fundamental to the academic review process, promotion and tenure at research institutions world-wide. Moreover, it is a requirement to obtain funding from the NIH and other funding agencies. Scientific journals are ranked according to their impact factors: the higher the factor, the more prestigious the journal. When applying for promotion or tenure, faculty members often present their publications in terms of impact factors to obtain a score high enough for consideration at their respective institutions.

When submitting peer-reviewed papers, a journal is selected, the paper is uploaded to that website, and an Editor or member of the Editorial Board sends the paper for review to colleagues in the field for comments, acceptance or disapproval. The higher the impact factor, the more stringent the review process. Reviewers for high-impact journals are generally not disclosed to the investigator submitting the paper and may suggest major or minor revisions before acceptance of the research for publication. In general, reviewers are asked to judge: 1) the significance of the study; 2) the appropriateness of the scientific methods used, including the numbers of samples, numbers of repeated experiments and necessary controls; 3) the methods for statistical analyses of data; and 4) the interpretation of data. Disclosure of conflicts of interest, i.e. whether or not the authors may have a financial or other bias in supporting or reporting their research results, and acknowledgements of research funding support, are required by almost all journals. After receiving reviews of one's submitted paper, the first listed or senior author can respond in a point-by-point fashion to suggested revisions or the need for additional experiments. These revisions are passed on to the original reviewers, who are asked to communicate their recommendations to the Editor and authors. The peer-review process for most journals may take several months, depending on needed additions and editorial decisions.

**Table 1** shows impact factors for several journals in the scientific literature.

**Table 1. Impact factors for scientific journals**

<b>Journal:</b>	<b>Impact Factor:</b>
<i>New England J. of Medicine</i>	79.260
<i>Science</i>	41.058
<i>Proceedings of the National Academy of Sciences</i>	9.504
<i>Cancer Research</i>	9.130
<i>Particle and Fibre Toxicology</i>	6.105
<i>Gynecologic Oncology</i>	4.540
<i>American J. Respiratory Cell &amp; Molecular Biology</i>	3.785
<i>Reproductive Sciences</i>	2.548
<b>(Science Citation Index, 2017)</b>	

In contrast to peer-reviewed scientific publications, other publications such as abstracts, book chapters, case reports, Updates or Reviews, Letters to the Editor, and Commentaries are generally not formally reviewed by peers in the scientific community before publication. Hence, scientific inaccuracies and flaws in interpretation of data can occur.

In addition to publishing in the peer-reviewed scientific literature, it is important to participate on interdisciplinary scientific panels that address important health and regulatory questions. In the field of asbestos-induced diseases, I have served on panels for months and years with toxicologists from industry, academia and government, geologists, biostatisticians, clinicians, dosimetry experts, pathologists and molecular biologists to gain an appreciation of how asbestos minerals cause disease.

## **V. Principles Of Toxicology: Epidemiology, Animal And *In Vitro* Experiments**

“Toxicology” is broadly defined as the study of any agent that causes adverse changes in cells of the body. There are many manifestations of toxicity or injury to cells that occur when normal defense mechanisms are overwhelmed. As emphasized by Drummond et al. (2016), the toxicity of inhaled fibers such as asbestos is described by a **3D** paradigm that recognizes the importance of **Dose, Dimensions** (long fiber length and fine/narrow diameter) and **Durability** in cancer development by minerals. These fundamental tenets of toxicology and cancer development have been endorsed by many panels of scientists evaluating risks of asbestos fibers (e.g., IARC, 1989; IARC, 2012; NAS, 1984; NRC, 2006; Health Effects Institute, 1991; ATSDR, 2003; Institute of Medicine, 2009).

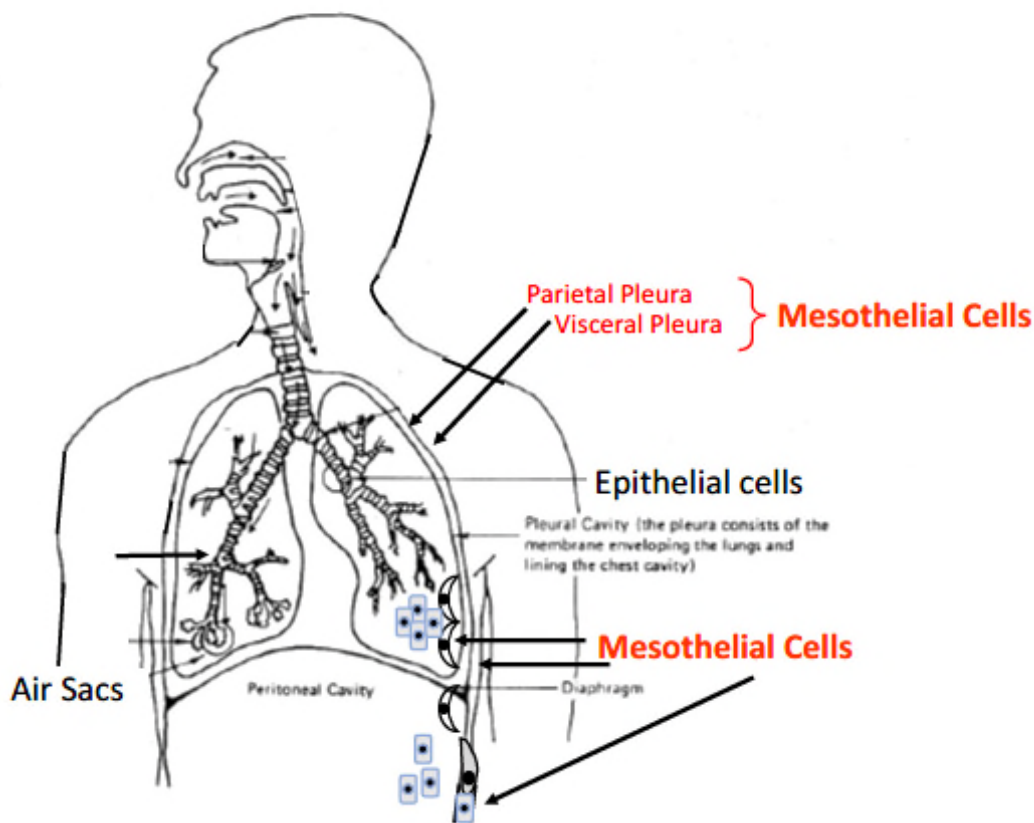
“Epidemiology,” the study of human populations, is often fundamental to assessing the health risks of minerals in occupational settings. However, because workers may be exposed to different types of minerals occupationally and environmentally and have a number of mineral types in their lungs, emphasis historically has been placed on results of studies in animals, i.e., *in vivo* experiments, where exposures to one mineral type can be assessed. As summarized by Drummond et al. (2016), an extensive database exists in rodents after inhalation, intratracheal instillation and intracavity injections of minerals (into the pleural or peritoneal cavities). Although inhalation experiments are the “gold standard” because they represent the natural route of exposure to inhaled particles, all methods are useful. For example, false positives (minerals that cause tumors in animals but not humans) may occur using intraperitoneal injections, but negative results exonerate a mineral from classification as a carcinogen (Drummond et al., 2016). This statement is of central importance to interpreting animal data on talc or cleavage fragments (see below).

*In vitro* experiments in which cell cultures and tissues (organ cultures) are kept outside of the body are also important models in toxicology. Exposures to defined concentrations and types of minerals can be examined in efforts to understand mechanisms of cancer causation and/or cell defense. It is important to use positive (known cancer-causing agents) and negative (non-cancer-causing agents) controls in these experiments when postulating mechanisms linked to cancer development. For example, any particle or fiber can be toxic to cells at very high concentrations due to mechanical injury.

## VI. Anatomy Of The Lungs And Pleura

An understanding of the architecture of the human lung is necessary to determine how lungs respond to inhaled materials. As diagrammed in **Figure 1**, inhaled particles enter through nasal passages. Some are swallowed, but the majority enter the airways through the tracheal tube that then branches into a series of progressively smaller airways (bronchioles). These tubes connect to the air sacs (alveoli) of the lung, where gases such as oxygen and carbon dioxide are exchanged.

**Figure 1. Diagram illustrating cell types of the human lung and pleura.**



The cells that line the trachea (main upper air tube), bronchioles and air sacs are called “epithelial cells” and can give rise to lung cancers, but primarily serve to protect the lung from foreign matter or allow gas exchange. These cells are supported by a matrix composed of cells called “fibroblasts” that can also thicken or multiply to give rise to the many forms of pulmonary fibrosis. This nonmalignant disease can be progressive and lethal in patients exposed to high (occupational) concentrations of asbestos, i.e., asbestosis. In contrast, talcosis, or fibrosis of the lungs, as demonstrated in some talc miners and millers, is different in its clinical features and pathology (Guthrie and Mossman, 1993 (*see chapter by Kane*)). It is **not** a malignant disease.



The pleural cavity consists of fluids around the lung and cells of the immune system that may accumulate in response to infection or foreign material. “Mesothelial cells” that line the lung are called visceral pleural mesothelial cells, and mesothelial cells that make up the outside sac enclosing the lungs are called parietal pleural mesothelial cells (see **Figure 1**). These cell types make mesothelial fluids that allow the lung to expand and contract during normal respiration. Mesothelial cells also line the peritoneal and pericardial cavities. Mesothelial cells give rise to mesotheliomas after exposures to certain amphibole asbestos types, radiation, and other asbestos-like minerals such as erionite and fluoro-edenite, but approximately 20% of patients with mesothelioma have no known exposures to these agents, and tumors may arise spontaneously or by genetic predisposition (Ilgren and Wagner, 1991; Sherwood et al., 2008; Testa et al., 2011).

#### **A. Inhalation and translocation of particles and fibers**

The diameter of particles governs whether they are inhaled and how deep in the lung they can penetrate (reviewed in Mossman et al., 2011). For example, fibers greater than 3 microns in diameter do not generally get inhaled, fibers > 1.5 microns in diameter do not penetrate the deep lung, and fibers > 0.5 microns in diameter do not get out to the pleura that line the lung (Lentz et al., 2003; McClellan et al., 1992).

#### **B. Natural defense mechanisms: How the lungs dispose of foreign particles (roles of macrophages and the lymphatics)**

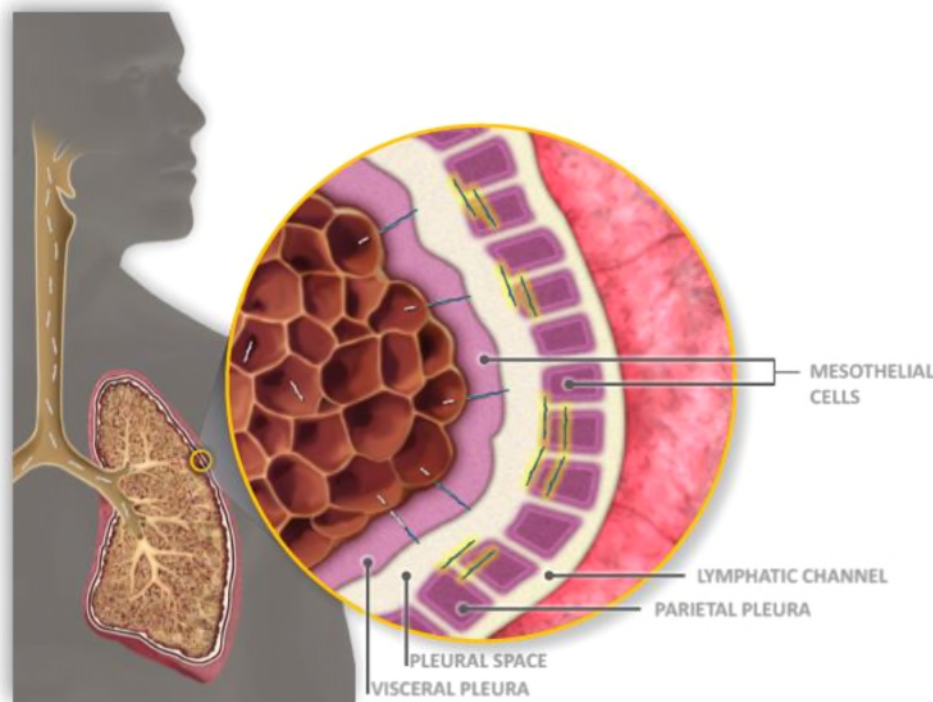
Cells called “macrophages” occur throughout the body, and populations of these cell types within the lung and pleura are called “alveolar” and “pleural” macrophages, respectively. These cell types arise from the bone marrow and can also multiply or change in function at sites of deposition of particles or microorganisms, processes linked to lung repair. The normal function of macrophages is to clear particles from the lung after they engulf them, a process known as “phagocytosis.” Particles or fibers that are effectively taken up by macrophages are cleared from the lungs as these cells move up the airways or enter the lymphatic system (see below). Many macrophages are propelled up and out of the lung by mucin secretions and hair-like cells called ciliated epithelial cells, often referred to as the mucociliary escalator. Other macrophages remain at sites of particle deposition and signal other cell types of the immune system, called “neutrophils” or “lymphocytes,” to accumulate and acquire immunity to combat toxic agents. The secretion of proteins called “cytokines” that signal to other cells of the immune system and cause these and other cell types in the area to proliferate or divide is a natural defense mechanism. However, many cytokines can also favor disease development if secreted in large amounts.

The lymphatic system consists of the lymph nodes and spleen, together with masses of lymphoid tissues in the respiratory tract and intestinal mucosa. The primary function of the lymphatic system is to provide immunologic defenses against foreign material. The lymph nodes serve as deposits for agents, and they are interconnected by lymphatic channels. “As the lymph fluids flow through the nodes, the phagocytic cells filter out and destroy any microorganisms that have gotten into the lymphatic channels” (Crowley, 2001). The lymphocytes (white blood cells within the node and elsewhere in the body) and macrophages also interact with the foreign material to

initiate an immune response. In the general population, many particles and fibers are found in lymph nodes throughout the body (Dodson et al., 2000).

Long, thin asbestos fibers can align themselves with airways and penetrate the deep lung to get to the pleura. Because of their large size, they are not effectively removed by normal clearance mechanisms, including alveolar macrophages, which cannot engulf or remove long fibers. At low concentrations, long fibers may pass through stomata to lymphatic channels for elimination. Stomata are channels approximately 10 microns in diameter that exist between mesothelial cells. At high concentrations of fibers, a bottleneck-like phenomenon occurs, whereby these channels are blocked, and fibers remain at sites of tumor development (Moalli et al. 1987; Murphy et al., 2011). In contrast, smaller fragments of minerals may drain out through the lymphatic system (see **Figure 2**).

**Figure 2. Diagram showing how long thin asbestos fibers become lodged at the pleural surface.**



### **C. Inflammation and repair (oxidants and antioxidants)**

The body has effective defense mechanisms for dealing with microorganisms and other potentially harmful substances. One mechanism is inflammation, “a nonspecific response to any harmful agent and includes phagocytosis of the material by neutrophils and macrophages” (Crowley, 2001). A first line of defense in inflammation is accumulation of macrophages and other cell types of the immune system in an orchestrated response to remove foreign materials. Importantly, we and others have characterized the inflammatory response in the lungs and pleura after inhalation of asbestos fibers and other materials and have shown that phagocytosis (i.e., cell uptake of these particles) results in intracellular and extracellular release of oxidants, often called reactive oxygen species (ROS) or reactive nitrogen species (RNS). Oxidants can interact with the DNA, lipids and proteins in cells to cause abnormal cell function.

We have characterized repair mechanisms in response to minerals, including a number of intracellular enzymes and proteins that are called “antioxidants” (Mossman et al., 1986; Shatos et al., 1997; Mossman et al., 1990; Janssen et al., 1990; Shull et al., 1991; Janssen et al., 1992; Holley et al., 1992; Janssen et al., 1993; Janssen et al., 1994; Mossman et al., 1996; Shukla et al., 2003; Mossman et al., 2011). At low exposure levels to minerals, antioxidants scavenge damaging oxidants, and effective repair is observed. However, at high concentrations of minerals, normal defense mechanisms can be overwhelmed. Dimensions and chemistry (i.e., iron content, availability and charge) are some of the factors driving production of oxidants (reviewed by Shukla et al., 2003).

#### **D. Chronic inflammation and foreign body carcinogenesis**

Chronic irritation and inflammation by cigarette smoke, asbestos and silica have been linked to the development of lung cancers (Kamp et al., 2011; Rakoff-Nahoum, 2006; Balkwill and Mantovani, 2002; Coussens and Werb, 2002). However, there is also evidence suggesting that inflammation and immune system stimulation inhibit the development of other cancers. Reviews on the topic emphasize that acute inflammation “is a beneficial response activated to restore tissue injury and pathogenic agents” (Landskron et al., 2014). Chronic inflammation over months and years can result in many diseases, including cancers, but has not been established as a cause of ovarian cancer – and there is evidence that is difficult to reconcile with the inflammation hypothesis (Ni et al., 2012). Notably, Rakoff-Nahoum (2006) cautions, “[t]he relationship between cancer and inflammation is not simple and cannot be reduced to one grand theory.”

We and others proposed that long, durable asbestos fibers in lungs and pleura served as “foreign bodies” in tumor development by acting as stimuli for frustrated cell uptake and continual release of oxidants (reviewed in Shukla et al., 2003; Kamp et al., 2011). We have also shown that oxidant release by high iron-containing crocidolite or amosite asbestos triggers abnormal cell responses and signaling pathways intrinsic to tumor development (reviewed in Mossman et al., 2011; Mossman et al., 2013). Moreover, we have prevented crocidolite asbestos-induced inflammation and hallmarks of disease development in both animals and *in vitro* models after administration of antioxidants (Mossman et al., 1986; Shatos et al., 1987; Mossman et al., 1990; Mossman et al., 1996).

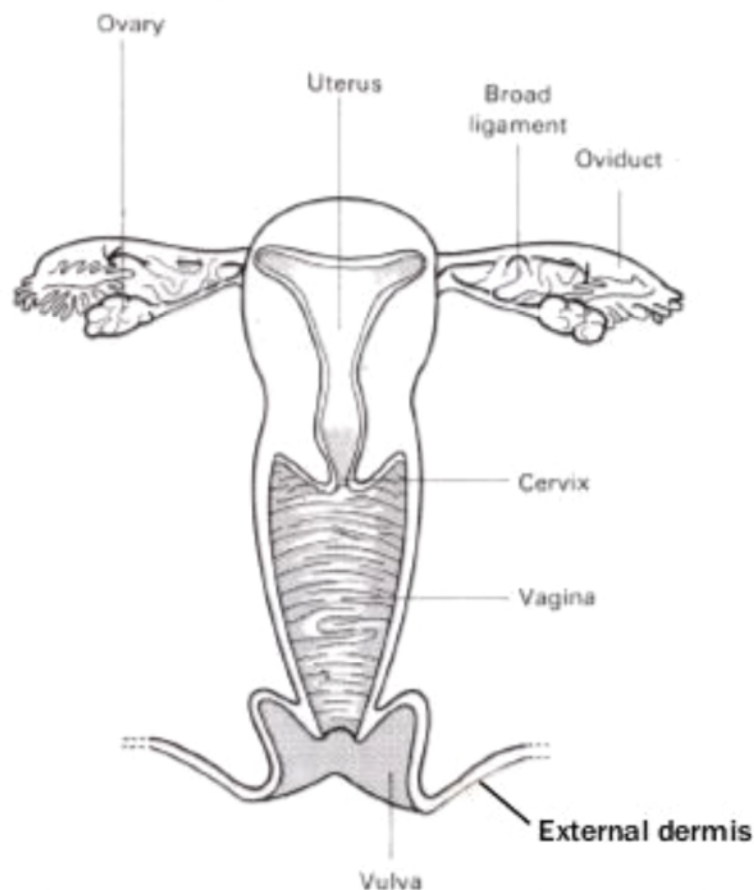
### **VII. Anatomy Of The Female Reproductive Tract And Barriers To Particles**

Protective surface mechanisms, tissue defenses including inflammation, and immune responses cooperate in protection of the female reproductive tract from disease-producing foreign matter. As illustrated in **Figure 3** below, the external genitalia are a first line of defense in that “the skin constitutes a relatively impenetrable barrier to most micro-organisms unless breached by injury such as abrasion or burning” (Burkitt et al., 1993, p. 191). The opening of the vagina is also enclosed by thick layers of skin (labia). Both muscular tissue and mucous layers similar to the mucociliary escalator of the respiratory tract line the vagina, uterus, and oviducts, and are protective against foreign matter.



Ovarian cancers develop from epithelial cells that line the ovaries and oviducts (Fallopian tubes). These structures are surrounded by a protective fibrous capsule. Ovarian epithelial cells are distinct from endometrial epithelial cells that line the uterus and give rise to endometrial cancers. Based upon these barriers, it is difficult to conceive of a route whereby talc, either after perineal dusting or inhalation, would reach and persist in epithelial cells in sufficient doses to cause ovarian cancers.

**Figure 3. Diagram of the female reproductive system (modified from Burkitt et. al., 1993).**



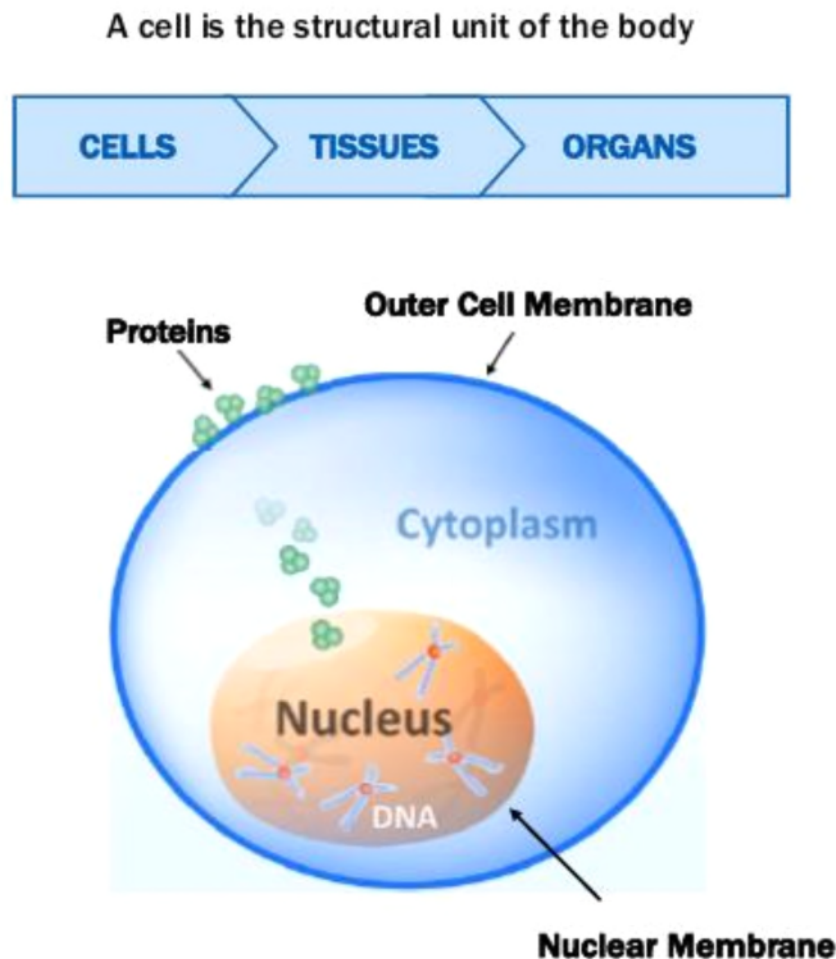
## **VIII. Cancer Development**

### **A. What is a normal cell and how is a cancer cell altered?**

The human body has billions of cells that serve a number of roles in maintaining the function of the human body, i.e., normal physiology. The cell is the building block of tissues and organs, and where cancers begin. Since changes in normal cell function can result in cancers, it is important to understand the fundamental structures of the cell and how they are altered in cancer. **Figure 4** is a diagram of a cell that illustrates the various organelles, i.e., intracellular structures important

in normal cell function. The cell is surrounded by an external membrane that encloses the two main compartments of the cell: 1) the nucleus, which contains the genetic material or DNA that is packaged into genes, and 2) the cytoplasm, in which organelles controlling cell respiration and other functions occur. Historically, scientists have focused on the DNA in the nucleus and how it is processed through the formation of RNAs to proteins that give rise to abnormal cell function. It is recognized that both genetic alterations to DNA and epigenetic changes (i.e., those that do not affect the DNA structure) are important in cancer development. **Figure 4** also shows proteins comprising receptors on the external cell membrane and occurring in cascades within the cells that are the focus of most current cancer research because they are altered in cancer development.

**Figure 4. Diagram of the components of the cell.**



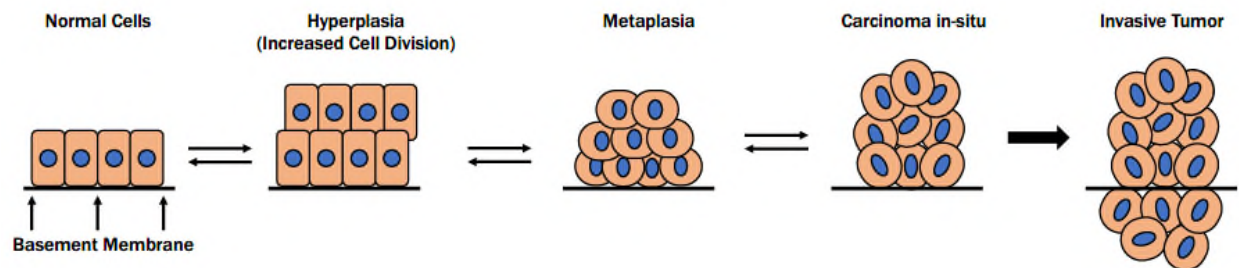
### **B. Stages of cancer development**

Cancer is “a disease of abnormal gene expression” characterized by uncontrolled cell proliferation or division and abnormal differentiation, i.e., altered cell function (Coleman and

Tsongalis, 2017). Consistent with epidemiologic studies showing that asbestos-associated cancers of the lung and pleura develop over many decades, examination of animal tissues and cells exposed to asbestos fibers show a sequence of events as they progress from normalcy to malignancy.

The stages of development of human cancers from epithelial cells in lung or ovarian malignancies called “carcinomas” are illustrated in **Figure 5**. The process begins by uncontrolled cell proliferation (hyperplasia) and proceeds to metaplasia, defined as a loss of normal cell function. These changes can be reversible, but as cells become progressively more abnormal (defined as dysplastic), they acquire further traits (increased survival, decreased resistance to programmed cell death and ability to grow under adverse conditions) that allow them to become malignant, i.e., a carcinoma-in-situ or tumor. Many carcinomas eventually invade normal tissues and metastasize to other organs. It is important to note that the reversible changes of cell proliferation and metaplasia by asbestos fibers can be documented in *in vitro* models, but whether these result in malignant tumors can only be assessed in animal studies.

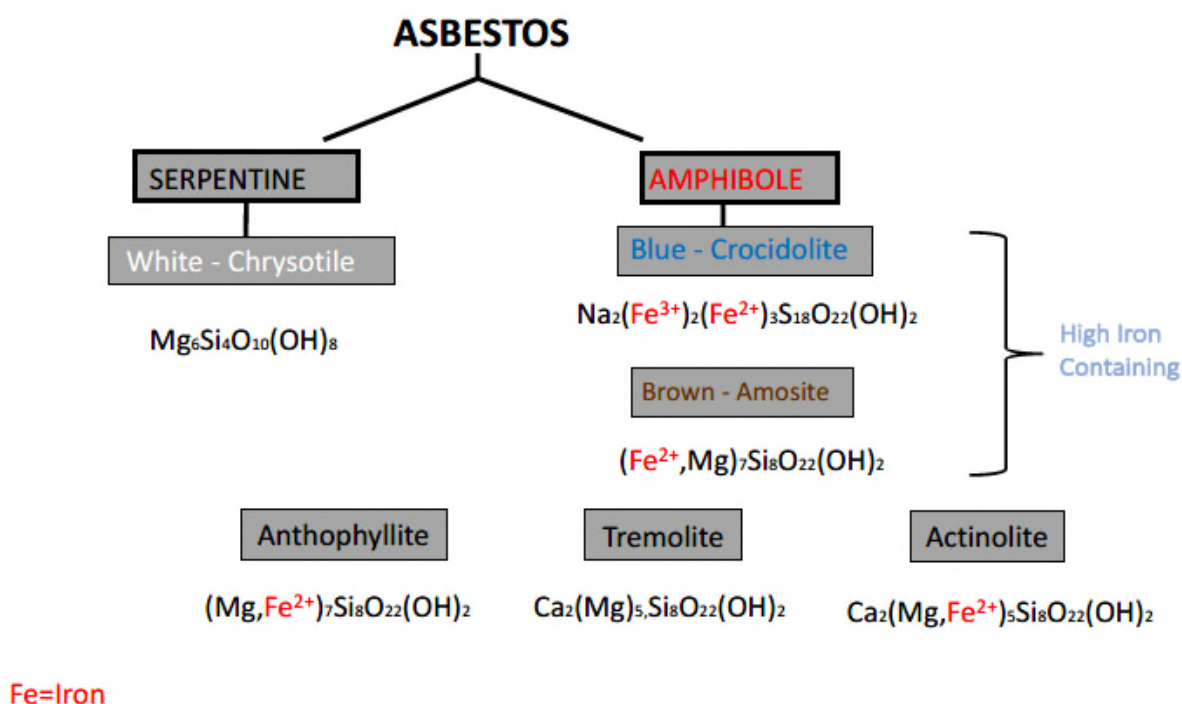
**Figure 5. Sequence of events leading to the development of human tumors i.e. carcinomas.**



## IX. What Is Asbestos?

“Asbestos” is a commercial term that refers to two groups of minerals that crystallize in a certain formation or habit called “asbestiform” (**Figure 6**). “Asbestiform implies relatively small fiber thickness and large fiber length, flexibility, easy separability and a parallel arrangement of the fibers” (Guthrie and Mossman, 1993). There are five asbestos types (crocidolite, amosite, anthophyllite, tremolite and actinolite) in the amphibole group of asbestos and one type (chrysotile) in the serpentine group. These differ in their chemical composition (as indicated on Figure 6) as well as their mineral crystallization structure and other features.

**Figure 6. Classification and composition of different asbestos types.**



#### **A. Epidemiologic studies showing different cancer risks of asbestos fibers in worker populations**

Since asbestos fibers have been mined and used in industries worldwide for more than a century, it has become apparent that workers exposed to different types of asbestos have different risks of lung cancers and mesotheliomas. A striking confounder in analysis of lung cancer data is the fact that almost all asbestos workers historically have been smokers, which is an overriding factor in causation of lung tumors, but studies on mesothelioma, a tumor not influenced by smoking, have been informative in ranking risks of mesotheliomas by various types of asbestos. The increased risks of mesothelioma in crocidolite and amosite asbestos-exposed workers have been documented in many epidemiologic studies and are much higher than risks associated with exposures to chrysotile asbestos (reviewed in Craighead and Mossman, 1979; Mossman and Gee, 1989; Mossman et al., 1990; IARC, 1989; Health Effects Institute, 1991; Hodgson and Darnton, 2000). For example, the robust database on mesotheliomas in epidemiologic studies has recently been updated by Garabrant and Pastula (2018), who found that the relative potency of chrysotile:amosite:crocidolite was 1:83:376-fold. Data on relative risks of asbestos types in workers have resulted in the conclusion that “[a]lthough all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos” (IARC, 2012, p. 238).

**B. Importance of size, shape, chemistry and other characteristics of asbestos fibers in the cancer process – human tissues, animal studies and *in vitro* models**

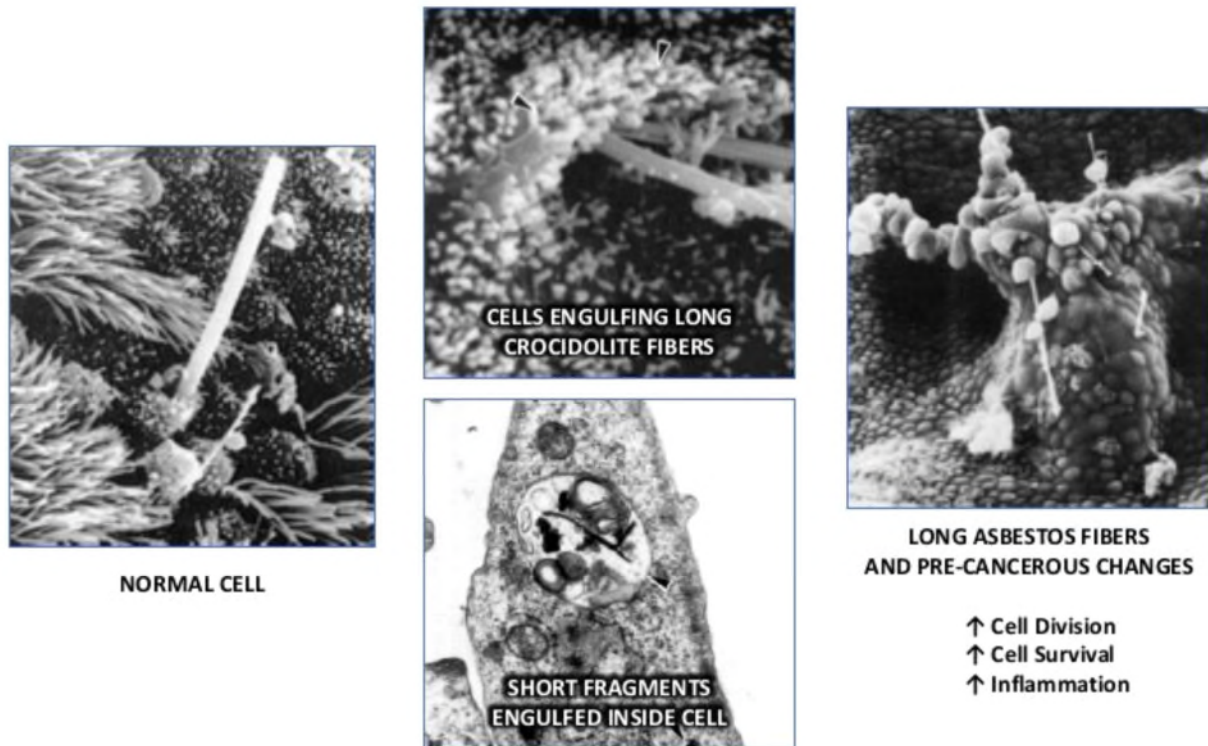
Fiber dimensions. Many properties of minerals are important in their toxicity and carcinogenicity. For example, more than a dozen different mineralogical features have been considered in developing a general model for predicting the cancer risks of mineral fibers (Gualtieri, Mossman and Roggli, 2017). Of these many properties, dimensions have been studied most extensively. Since the pleural injection studies of Stanton et al. (1981) who calculated in rodents that fibers > 8 microns in length and <.25 microns in diameter were most carcinogenic, it has been recognized that long, thin fibers are associated with chronic inflammation, lung cancers and mesotheliomas in rodents and humans (reviewed in Barlow et al., 2018; Roggli, 2015; Lippmann, 2014). For example, length-dependent retention of fibers, inflammation and injury has been demonstrated in animals exposed to a number of fiber types (Moalli et al., 1987; Donaldson et al., 1989; Donaldson et al., 2010; Murphy et al., 2011; Murphy et al., 2012; Schinwald et al., 2012; Murphy et al., 2013). Carcinogenicity studies using long vs. short fiber preparations in rodents also show that long fibers preferentially cause mesotheliomas and lung cancers (Pott, 1978; Davis et al., 1978; Spurny et al., 1979; Stanton et al., 1981; Davis et al., 1986; Berman et al., 1995; Chernova et al., 2017).

In the studies above, the cut-off value length of long fibers associated with tumor development was > 5 microns, as fibers of these dimensions have been measured in most studies by microscopy conducive to regulatory definitions. However, it has been emphasized recently that fibers 10 microns or greater in length are more representative of carcinogenic potency in humans based on analysis of human tissues (Roggli, 2015; Roggli and Green, 2019). It also has been stressed that human macrophages are > 16 microns in diameter and cannot engulf and remove larger fibers effectively (reviewed in Oberdorster and Graham, 2018).

Our studies have shown that lung epithelial and mesothelial cell responses to long and short asbestos fibers are different. As shown in the left panel of **Figure 7** using electron microscopy, normal cells come in contact with both long and short fibers. However, cells cannot completely engulf (phagocytose) long asbestos fibers (upper middle panel), whereas short fragments are incorporated into intracellular membrane-bound digestive structures for removal. We have shown that industrial talcs (Woodworth et al., 1982; Shukla et al., 2009) and a number of other non-disease-causing minerals, including cleavage fragments, are taken up by lung epithelial and mesothelial cells in a similar manner without causing toxic effects. The right panel of Figure 7 shows that long asbestos fibers remain on the surface of exposed cells for months to stimulate inflammation, increased cell division and altered cell appearance (i.e., metaplasia) in organ (mixed cell) cultures of the lung.

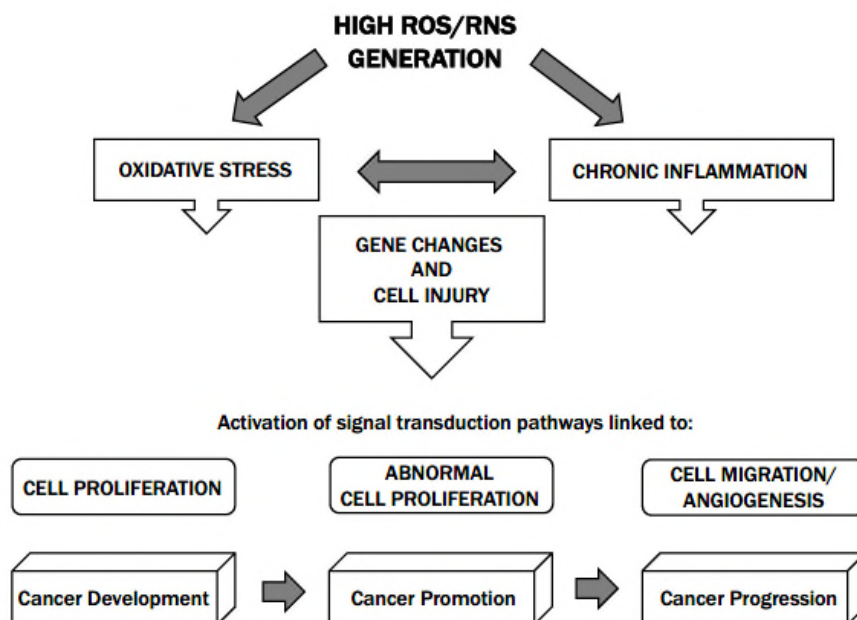


**Figure 7. Different mechanisms of lung and mesothelial cell response to long (>5 microns) or short (<5 microns) fibers.**



In other studies, we have documented that, in contrast to short fibers, long fibers (> 10 microns) cause significantly more oxidant release from macrophages (Hansen and Mossman, 1987; Mossman et al., 1989). Long fibers also stimulate membrane receptors and proteins linked to cancer development (Marsh and Mossman, 1988; Pache et al., 1998) as well as preneoplastic changes (Mossman et al., 1977; Woodworth et al., 1983 a,b,c). Others have shown that long fibers preferentially interact with chromosomes and cytoplasmic proteins affecting cell division (Cole et al., 1991; Ault et al., 1995; Jensen and Watson, 1999). **Figure 8** (adapted from Benedetti et al., 2015) shows links between oxidant generation and the development of cancers by crocidolite or amosite asbestos as demonstrated in our laboratory over the past 30-40 years. These show that high dose-dependent production of oxidants must occur over time to induce oxidative stress and alterations in gene/protein expression that activate cell signaling pathways leading to tumor development (reviewed in Shukla et al., 2009; Mossman, 2011; Mossman, 2013).

**Figure 8. Mechanisms of high oxidant generation and cancer development by asbestos fibers.**



Fiber shape. Unlike amphibole asbestos fibers, which crystallize in a straight, rodlike formation, chrysotile asbestos fibers form in tangled or helical bundles that impede their penetration into the finer airways and the deep lung. For these reasons, chrysotile fibers, in contrast to amosite or crocidolite asbestos, have diminished accumulation and persistence in lungs after inhalation (Wagner et al., 1976). It also has been shown that the dissolution or breakdown of chrysotile asbestos occurs due to the leaching of magnesium from fibers and separation of fiber bundles into smaller fibrils (reviewed in Mossman et al., 2011). This dissolution is also important in establishing why chrysotile asbestos is less durable in lungs and less apt to cause mesotheliomas in humans.

Fiber chemistry, flexibility, crystal structure and durability. In addition to the role of fiber dimensions and shape, other properties have been linked to mesothelioma development by amosite or crocidolite asbestos (reviewed in Mossman et al., 2011; Mossman et al., 2013; Shukla et al., 2003; Mossman, 2018). These include: 1) their high iron content, which drives production of oxidant species causing oxidation of DNA and stimulation of cell signaling pathways to malignancy; 2) surface availability of iron (Fe) in a form or surface charge that drives redox reactions. In this regard,  $\text{Fe}^{+3}$  on the surface of crocidolite asbestos drives chemical reactions producing toxic oxidants. Conversely, forms of iron such as ferritin, which comprises ferruginous bodies in the lung, do not drive these reactions and may be protective when minerals such as talc are coated by macrophages in the lung or pleura (Gualtieri, Mossman and Roggli, 2017); 3) flexibility or the ability of asbestos fibers to penetrate and move throughout the lung and pleura; 4) crystal structure and growth; and 5) ion exchange and dissolution. All of these properties affect fiber durability at sites of tumor development and the responses of cells to minerals (reviewed in Gualtieri, Mossman and Roggli, 2017).

### **C. Studies supporting the importance of dose, the existence of a threshold for asbestos-induced mesotheliomas, and other causes of mesothelioma**

As discussed in **Section VI.** above, the importance of dose-related responses in the development of cancers is a fundamental tenet of toxicology. Epidemiologic studies on asbestos-related mesotheliomas have demonstrated that dose and duration of exposure in workplace environments are linked to risks of tumor development. Moreover, animal experiments in our laboratory (Quinlan et al., 1994; Quinlan et al., 1995; Shukla, Vacek and Mossman, 2004) and others (reviewed in Health Effects Institute, 1991; Mossman et al., 2011; Drummond et al., 2016) have shown that both hallmarks of disease development and tumors are dose-related. In rodent studies using both chrysotile and crocidolite asbestos, we measured inflammation, molecular changes (elevations in expression of genes linked to cancer development) and proliferation in lung epithelial and pleural mesothelial cells for periods as long as 40 days after initiation of exposures to two concentrations of asbestos. These studies showed no significant changes by asbestos types at concentrations far exceeding current occupational exposure limits set by regulatory agencies such as NIOSH.

*In vitro* experiments also show thresholds below which aberrations do not occur in response to various asbestos types (DiPaolo et al., 1983; Jaurand et al., 1986; Mikalsen et al., 1988; Oshimura et al., 1984; Palekar et al., 1988; Price-Jones et al., 1980). Thus, both *in vivo* and *in vitro* results indicate the existence of a threshold below which cell and tissue responses are not observed (reviewed in Mossman, 2018; Ilgren and Browne, 1991). These studies undermine the theory that a single or low dose of a carcinogen-causing mineral gives rise to cancer.

Many reports and reviews indicate other causes of mesotheliomas, including radiation and other mineral fibers such as erionite and fluoro-edenite (reviewed in Ilgren and Wagner, 1991; Kane, 1996; Gualtieri et al., 2018; Kraynie et al., 2016). Factors such as genetic predisposition (Testa et al., 2011; Ohar et al., 2016; De Rienzo et al., 2016), aging and spontaneous transformation of normal cells to genetically unstable or tumor cells (Fleury-Feith et al., 1989; Sherwood et al., 2008; Funaki et al., 1991) may also occur. These factors may explain the 15 to 20% of mesotheliomas occurring in individuals with no documented exposures to asbestos fibers (Kraynie et al., 2016; Attanoos et al., 2018).

### **X. What Is A Cleavage Fragment?**

“Cleavage” is defined as “the property of an individual crystal to fracture or break along crystallographically defined planes determined by the structure of a mineral” (Guthrie and Mossman, 1993). Defined broadly, cleavage fragments can occur when amphiboles and other minerals are milled or crushed, but not after crushing of other materials, such as chrysotile asbestos or synthetic glass. It is important to realize that amphibole minerals “occur more commonly in a non-asbestiform habit [i.e., crystallized form], and may also be elongated [i.e., fibrous] without being asbestiform” (IARC, 2010, p. 277). Plaintiffs’ expert Mark Krekeler has opined that nonasbestiform minerals such as tremolite and anthophyllite that break into cleavage fragments during processing become “asbestiform particles with the same health risks as asbestos, due to the size, morphology and chemistry of the modified particles” (Krekeler Report,



pp. 3-4). This is not scientifically accurate. Cleavage fragments are not asbestiform and **not asbestos** by definition. The classification and nomenclature of respective asbestos types and their nonasbestos cleavage fragments are indicated in **Table 2**. Further, reliable studies demonstrate that exposure to cleavage fragments is not associated with the development of mesotheliomas or cancers (Addison and McConnell, 2008; Gamble et al., 2008; Chatfield, 2018; Garabrant and Pastula, 2018; Roggli and Green, 2018).

**Table 2. Classification of asbestos fibers and non-asbestiform fragments**

MINERAL FAMILY		ASBESTOS ASBESTIFORM	NON-ASBESTIFORM (including cleavage fragments)
Serpentine		Chrysotile	Antigorite/Lizardite
		Crocidolite	Riebeckite
		Amosite	Cummingtonite-Grunerite
Amphibole		Tremolite Asbestos	Tremolite
		Anthophyllite Asbestos	Anthophyllite
		Actinolite Asbestos	Actinolite

#### **A. Different properties of cleavage fragments and amphibole asbestos fibers**

Cleavage fragments differ from their asbestos counterparts in several important respects (**Table 3**). Most importantly, they differ in their dimensions because they cleave into blunt, thick fragments as opposed to amphibole asbestos, which breaks longitudinally into long, thin fibers. As discussed above, the diameter or width of fibers governs whether they are inhaled and how deep in the lung they can penetrate (reviewed in Mossman et al., 2011). For example, fibers > 3 microns in diameter do not generally get inhaled; fibers > 1.5 microns in diameter do not penetrate the deep lung; and fibers > 0.5 microns in diameter do not get out to the parietal pleura (Lentz et al., 2003). Measurements on cleavage fragment preparations show that fragments > 10 microns in length do not have widths < 0.5 microns, and thus will not get out to the pleura. Moreover, less than 0.05% of long cleavage fragments have widths < 0.25 microns (Wylie, 2016; email exchange with Dr. Wylie). Thus, amphibole cleavage fragments are unlikely to be inhaled or penetrate to the pleura, where mesothelial cells exist. The overall dimensions of cleavage fragments are also incompatible with the dimensions of amphibole asbestos fibers shown to be important in tumor development (Wylie, 2016; Roggli and Green, 2019).

### **Table 3. Properties of asbestos minerals important in cancer development**

- **Dimensions (Long, Thin)**
- **Geometry (Rod-like)**
- **Crystal Structure and Growth**
- **Flexibility/Tensile Strength**
- **Chemical Composition**
- **Surface Area/Chemistry/Charge**
- **Durability\***

**\* All these properties are interlinked to persistence of fibers at sites of cancer development.**

Important differences in dose-responses to asbestos and cleavage fragments exist because unlike asbestos fibers, nonasbestos fragments do not break in a parallel fashion to create more long and thin fibers. There are also differences in flexibility between asbestos and nonasbestos fragments due to differences in their crystalline structure and growth. These factors may influence how cells respond to these materials. Lastly, crocidolite asbestos and its respective cleavage fragment, riebeckite, are different in that crocidolite asbestos generates oxidants via its iron content. Guthrie (1997) emphasizes the significant replacement of oxidant-generating iron by magnesium in riebeckite as compared to crocidolite asbestos. The dissolution of riebeckite by this process could also reflect a lack of durability of riebeckite fragments. Gunter et al. (2011) have also shown differences in iron chemistry of asbestiform and nonasbestiform amphibole minerals that explain why asbestiform amphiboles have more oxidant-generating capabilities. Lastly, surface defects and surface chemistry are different, and these factors are important in reactivity with cells (see below).

#### **B. Animal studies demonstrate no cancers after exposures to cleavage fragments.**

Chronic lifespan studies in rodents after administration of asbestos or nonasbestos fragments by a variety of routes have failed to demonstrate the development of mesotheliomas by cleavage fragments (**Table 4**). Most relevant to this discussion is a recent EPA study in which a number of naturally occurring asbestos types and an asbestos-like amphibole mineral from Libby, Montana were injected directly into the trachea of rats at two concentrations (Cyphert et al., 2015; Cyphert et al., 2016). Tumors occurred after exposures to the Libby amphibole, described as a transitional

asbestiform fiber, at high concentrations of minerals (i.e., millions of fibers) but not at 10-fold lower concentrations. In contrast, an iron-containing nonasbestos fragment, i.e., ferroactinolite, did not cause lung injury or tumors. This study indicates that it is not iron content *per se* that causes oxidant production, inflammation and injury. Moreover, results support the tenet of a threshold concentration of minerals below which tumors do not occur.

**Table 4. Life time rodent studies show no mesotheliomas nor ovarian cancers after exposures to non-asbestos cleavage fragments and talcs**

Study	Asbestos	Non-Asbestos Fragment*
Stanton and Wrench 1972,1981	All amphiboles +	Fibrous and platy talcs -
Wehner et al. 1972		Cosmetic talc -
Wagner et. al. 1975	Chrysotile +	Italian talcs
Stenback + Rowland, 1978		Fibrous talc -
Wagner et. al. 1980	Crocidolite +	Talc -
Wagner et al., 1982	Tremolite +	Tremolite -
Smith et. al., 1979		Fibrous talcs -
McConnell et al., 1983 (feeding studies)	Tremolite -	Tremolite -
Coffin et al., 1992	Amosite +	Grunerite -
Cyphert et al., 2016	Libby amphibole +	Ontario ferroactinolite -

**C. *In vitro* studies demonstrate that cleavage fragments do not induce oxidant production and markers of inflammation and cancer development.**

We have traditionally used cleavage fragment preparations of riebeckite in our *in vitro* models to determine whether mechanisms of action of crocidolite asbestos are unique or observed after exposures to particles in general. For these reasons, we have also used a number of nonasbestos fibers and particles to determine the properties of crocidolite and amosite fibers that are important in cell responses. Erionite and Libby amphibole fibers have been used as positive controls, i.e., minerals that induce cancer, and a number of particles not associated with cancer development, such as glass beads, titanium dioxide and polystyrene beads have been used as negative controls. In all studies, we and teams of geologists characterized the shape, dimensions and other characteristics of minerals and their toxicity to cells.

Experiments using crocidolite and nonasbestos riebeckite comparatively are listed in chronological order in **Table 5**. These studies generally focused on whether crocidolite, as compared to riebeckite, caused changes in oxidant generation, oxidative damage to cells, and signatures of early cancer development, including increased cell division and loss of normal function, i.e., metaplasia. In summary, studies on lung epithelial cells and mesothelial cells showed responses that were specific to crocidolite asbestos fibers and not observed with riebeckite fragments.

**Table 5. Studies showing the lack of oxidative stress, inflammation and hallmarks of cancer development by non-asbestos fragments including talcs (Mossman laboratory in peer-reviewed literature)**

Study	Asbestos Fibers	Non-Asbestos Fragments
Woodworth et al., <i>Cancer Res.</i> , 1983, Cell Division, Metaplasia	Crocidolite +	Riebeckite
Hansen and Mossman, <i>Cancer Res.</i> , 1987, Oxidant release	Crocidolite +	Riebeckite
Marsh and Mossman, <i>Cancer Res.</i> , 1988, Tumor promoting protein	Crocidolite +	Riebeckite
Heintz et al., <i>PNAS USA</i> , 1993, c-fos, c-jun, AP-1	Crocidolite +	Riebeckite
Janssen et al., <i>Am. J. Resp. Crit. Care Med.</i> , 1994, Antioxidant enzymes	Crocidolite +	Riebeckite
Janssen et al., <i>Am. J. Resp. Cell Mol. Biol.</i> , 1994, Early response genes	Crocidolite +	Riebeckite
Zanella et al., <i>Cancer Res.</i> , 1996, ERK1/2 Proteins	Crocidolite +	Riebeckite
Chen et al., <i>Carcinogenesis</i> , 1996, Oxidative DNA damage	Crocidolite +	Riebeckite
Janssen et al., <i>Am. J. Path.</i> , 1997, Cell survival protein	Crocidolite +	Riebeckite
Goldberg et al., <i>Am. J. Resp. Cell Mol. Biol.</i> , 1997, Programmed cell death	Crocidolite +	Riebeckite
Wylie et al., <i>Toxic. Appl. Pharm.</i> , 1997, Cell survival	Crocidolite +	NYS Talc* (11%, 37%, 59% fibers)
Zanella et al., <i>Am. J. Physiol.</i> , 1999, Cell receptor interference	Crocidolite +	Riebeckite
Shukla et al., <i>Am. J. Resp. Cell Molec. Biol.</i> , 2009, Increased gene expression	Crocidolite +	Talc
Hillegass et al., <i>J. Toxic. Environ. Health</i> , 2010, Differential gene expression	Crocidolite +	Talc
Taylor et al., <i>Langmuér</i> , 2013, Receptor stimulation	Crocidolite +	Riebeckite

## **XI. What Is Talc?**

### **A. Different properties of talcs and asbestos fibers**

Talc can be considered a cleavage fragment in the broadest use of this term because it is milled and crushed during and after mining. However, it should be emphasized that talc is distinct in form and chemical composition from amphibole cleavage fragments or chrysotile asbestos (Guthrie and Mossman, 1993). In this regard, its molecular formula contains magnesium and silica, but its crystalline structure is dissimilar. Unlike amphibole asbestos, which can persist in the body for the decades required for human tumor development, the estimated retention time for a talc particle in the body is approximately eight years (IARC, 2010, p. 281). Talc is insoluble (thus not to be confused with a chemical) and “has very little chemical reactivity” (IARC, 2012, p. 230). It has no positive charge, a factor linked to toxicity of chrysotile asbestos in many cell types (Craighead et al., 1980; Woodworth et al., 1982). In contrast to asbestos fibers, the shape of talc particles is plate-like and rarely fibrous. Fibrous talcs occur in some ores, such as those occurring in the Gouverneur mining districts of New York, that have not been exploited commercially for production of cosmetic or pharmaceutical talcs (IARC, 2010, p. 281; Wylie et al., 1997). In any event, as set forth below, there is no scientifically reliable evidence that fibrous talc is carcinogenic or that exposure to fibrous talc poses a health risk similar to that which is associated with asbestos fibers. Fibrous talcs not containing asbestos fibers have **not** been classified as human carcinogens (IARC, 2010, p. 412) and are structurally and chemically different from asbestos or asbestiform fibers.

Commercial talcs can be described as industrial (referring to mining samples or products containing minerals other than talc), cosmetic talcs that are more pure (> 98% talc) and pharmaceutical talcs (> 99% pure) used for medical procedures such as pleurodesis (IARC, 2012, p. 230; Zazenski et al., 1995). In the United States, the presence of asbestos in talc has been documented in a mining deposit in Death Valley, CA that has never been used for processing of cosmetic or pharmaceutical talcs (Van Gosen et al., 2004). Talc in the body does not have the same inflammatory and carcinogenic effects as amphibole asbestos fibers because of its different properties and purity.

### **B. Numerous studies in animals and humans exposed to high levels of industrial, cosmetic and pharmaceutical talcs do not demonstrate the development of mesotheliomas.**

**Table 4** above summarizes the results of life-time rodent studies designed to test whether administration of industrial or cosmetic talcs via a number of routes is cancer-causing. These and other studies summarized in IARC (2010) have evaluated the carcinogenicity of various talcs at high concentrations after inhalation or injections. Regardless of the route of exposure, studies using platy or fibrous talcs have failed to demonstrate tumor development. The results of animal studies have also been supported by epidemiologic studies in talc miners and millers that show no increased risk of mesothelioma (Rubino et al., 1976; Rubino et al., 1979; Coggiola et al., 2003; Addison and McConnell, 2008; Gamble and Gibbs, 2008; Anderson et al., 2017; Boffetta, 2018; Garabrant and Pastula, 2018; Pira et al., 2018).



Long-term follow-up of individuals after injection of pharmaceutical talcs into the pleural cavity also shows no inflammatory disease or tumors. Injection of talc particles into the pleural cavity has been used in treatment of human pleurodesis (collapse of the lungs) and to combat malignant effusions. This causes a transient inflammation and release of inflammatory cytokines that seal the damaged pleura. Multiple follow-up studies show that no mesotheliomas or ovarian cancers develop subsequently in persons undergoing these procedures (Clive et al., 2016; Kolschman, 2005; Hunt et al., 2007).

**C. *In vitro* studies demonstrate that talc does not cause markers of inflammation and tumor development.**

Studies by others have shown that talcs from various mining sites do not induce DNA damage or signatures of genotoxicity associated with initiation and development of mesotheliomas (Endo-Capron et al., 1993). Our experiments subsequently examined whether talc particles played a role in increased cell survival and proliferation of rodent lung epithelial and mesothelial cells (Wylie et al., 1997). We also measured injury to cells as indicated by decreased cell survival.

In these experiments, we added reference samples of crocidolite or chrysotile asbestos or 3 samples of New York fibrous industrial talcs. The total percentages of fibers were 11, 37 and 59 in talc preparations, and the mineral composition, chemistry, crystal structure and size of minerals were documented by geologists at Yale University and the University of Maryland. Samples of fibrous talcs also contained cleavage fragments of nonasbestiform tremolite and anthophyllite.

In brief, talcs and asbestos at multiple concentrations were added to cells for seven days, and the size of colonies of cells developing over this time period (an indication of cell survival) were measured. Rat mesothelial cells did not exhibit increased cell survival in response to either asbestos or talc samples, which was attributed to shortcomings of this assay when evaluating growth of individual cells in culture. However, exposures to both asbestos types caused increased survival of lung epithelial cells, whereas talc fibers did not, even when doses of fibers were controlled for approximately equal amounts of fibers > 5 microns in length, equal surface areas and other dose parameters. Thus, the proliferative responses we observed with asbestos could not be explained by differences in fiber dimensions or surface areas. These results indicate an important role of mineralogical composition and type, as opposed to dimensions alone, in induction of precancerous changes. Our results correlated with data on tumor development after injection of asbestos, New York talcs and other talc samples into animals (Smith et al., 1979; Stanton et al., 1981). Despite doses of talc fibers > 8 microns in length and < 0.25 microns in widths large enough to predict a tumor probability of > 50%, no excesses in tumor development were observed (Stanton et al., 1981). These studies also indicate that cleavage fragments of nonasbestiform tremolite and anthophyllite are not carcinogenic.

In subsequent research, we have examined the gene expression changes by crocidolite asbestos in comparison to a well-characterized platy industrial talc, glass beads and titanium dioxide (both non-cancer-causing particles, i.e., negative controls) in human mesothelial and ovarian epithelial cells (Shukla et al., 2009; Hillegass et al., 2010). After examining a range of concentrations of all

materials to determine toxicity, we used a low and high concentration of asbestos at eight hours to determine whether dose-responses in gene expression occurred in comparison to equal surface area concentrations of talc, glass beads and titanium dioxide particles. Cell death precluded the analysis of gene expression by high concentrations of asbestos at 24 hours; thus, talc at comparable high concentrations was not examined at this time point.

Results are presented in **Table 6**. In mesothelial cells, gene expression analyses in comparison to untreated control cells (no particle added) showed that changes in gene expression were dose-related and increased over time at low concentrations of asbestos. In contrast, talc produced less striking increases in gene expression that decreased over time. Unlike asbestos, talc did not down-regulate any genes. Ovarian epithelial cells were more resistant to toxicity and gene changes by asbestos, and no significant changes in gene expression were observed with talc. Glass beads and titanium dioxide did not induce significant gene changes in either cell type. Lastly, we performed experiments to determine the function of a specific gene (ATF3) that was significantly upregulated by talc at eight hours and asbestos at both time points to determine its functional role in inflammation. By blocking the expression of this gene in freshly isolated pleural mesothelial cells, we prevented the production of several proteins linked to asbestos-induced inflammation and cancers. Thus, ATF3 was characterized as a gene/protein that is anti-inflammatory and inhibits early markers of cancer development by asbestos.

A follow-up of this study showed that gene expression by talc was significantly different both qualitatively and quantitatively from asbestos (Hillegass et al., 2010). Another sophisticated method was used to compare dose and time-related patterns of talc-induced gene expression in relationship to asbestos (positive control) and glass beads/titanium dioxide (negative controls). These methods reconfirmed that gene expression by talc was equivalent to gene expression by non-cancer-causing control particles and untreated cells (no particle exposures) in human mesothelial cells and ovarian epithelial cells. In our experiments, gene expression was compared to respective protein expression and release in cells and did not correlate precisely. Thus, our results emphasize, as do many studies in the literature, that it is imperative to measure whether changes in genes (SNPs, etc.) correlate with levels, release and activity of proteins in mechanistic *in vitro* studies.

**Table 6. Talc does not cause altered gene expression in human mesothelial or ovarian epithelial cells**

<u>Groups</u>	<u>Mesothelial Cells</u>		<u>Ovarian Epithelial Cells</u>	
	24 hrs	8 hrs	8 hrs	24 hrs
<b>1. Asbestos</b>				
Low*	29	205	0	0
High	236	– Cell Death	2	17
<b>2. Talc</b>				
Low	1	0	–	–
High	30	–	0	0
<b>3. Fine TiO<sub>2</sub></b>				
Low	0	0	–	–
<b>4. Glass Beads</b>				
High	0	0	0	0
<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="font-size: 4em;">}</div> <div>N.S.</div> <div style="font-size: 4em;">}</div> <div>N.S.</div> </div>				

\* = Low concentration = 1µg/cm<sup>2</sup>; High concentration = 5 µg/cm<sup>2</sup>.  
 – = Not examined  
 N.S. = Not significant statistically

In summary, my research data, review of the peer-reviewed scientific literature and relevant panel conclusions do not support the premise that either platy or fibrous talc causes mesotheliomas, lung cancers (in the absence of smoking) or ovarian cancers in animals or humans.

## **XII. Scientific Evidence Does Not Support The Hypotheses And Opinions Of Dr. Saed.**

Qualifications: Ghassan Saed, Ph.D., has been an Associate Professor at Wayne State University for approximately 20 years. Dr. Saed testified that he has not applied to be a full professor because his institution “requires current NIH NCI only funding, which is very hard to get” (Saed Dep. Vol. I 279:11-17), but this explanation glosses over other, more fundamental weaknesses in Dr. Saed’s resume, most notably a lack of independent research funding and sporadic publications in low-impact journals. He states, “My laboratory investigates the role of oxidative stress in the pathogenesis of ovarian cancer” (Saed Report, p. 2). This research is limited to a few publications on identification of early markers of disease, and the roles of oxidative stress in chemoresistance exhibited by epithelial ovarian cancer cells (EOC). An Update/Review of the literature summarizes roles of oxidative stress at various stages of ovarian cancer development, but does not address talc (Saed, Diamond and Fletcher, 2017). Sources of funding are not disclosed on his “Update” article, which largely serves as the basis of his opinions on talc. It is



unclear whether this review, listed at least twice on his CV and multiple times in his report, was peer-reviewed. The funding sources of his past and current research on the development of ovarian cancers are unclear, and he is not listed as principal investigator on federal grants supporting his research. His CV lists several grants as pending or active that in fact should be expired according to their dates, and many others that have not been funded (Saed CV, pp. 21-26). In his January 23, 2019 deposition, Dr. Saed clarified that his time spent on talc research and the resulting article on the “molecular basis” of ovarian cancer were funded by plaintiffs’ counsel.

Dr. Saed’s sole membership historically on editorial boards for journals is limited to “Editor-in-Chief, Gynecology and Obstetrics Research-Open Journal- 2015-Present.” This journal is not indexed in PubMed (the largest research database in medical literature). Nor does it report an impact factor. This is highly unusual.

As outlined below, Dr. Saed’s opinions are not supported by his publications or others in the fields of toxicology and ovarian cancer development. His review of the literature is questionable, as many of his statements are unreferenced, referenced incorrectly, or listed, but not discussed in the text. Likewise, results and conclusions from peer-reviewed studies are often misconstrued or omitted if contrary to his opinions.

Ovarian Cancers: In his report, Dr. Saed states that the “pathophysiology of EOC is not fully understood but has been strongly associated with inflammation and the resultant oxidative stress” (Saed Report, p. 4 (citation omitted)). The reference cited is a general review article entitled “Oxidative stress, inflammation and cancer: How are they linked?” (Reuter et al., 2010). There is no mention of ovarian cancer in the text of this article. A citation by Chan et al. (2008) in Table 2 of Reuter et al. (2010) describes a signaling pathway mediated by oxidative stress that “enhances tumorigenicity and chemoresistance of ovarian cancer cells,” but these effects occur after cells have become malignant and are irrelevant to the **causation** of ovarian tumors. It should be acknowledged that Reuter and colleagues discuss the mechanisms “by which **continued** oxidative stress can lead to **chronic** inflammation, which in turn could mediate most chronic diseases including cancer, diabetes, and cardiovascular, neurological and pulmonary diseases” (Reuter et al., 2010, Abstract), and never mention talc as an agent inducing oxidants or cancers. In fact, inflammation has not been linked to the development of ovarian cancer, which explains why Dr. Saed is not able to cite any publication supporting that statement.

Sections on Oxidative Stress and Ovarian Cancer Cells Manifest a Persistent Pro-oxidant State in Dr. Saed’s report describe the importance of the balance between oxidative stress and antioxidant repair mechanisms. The statement on page 5, “[r]ecent evidence demonstrates that oxidative stress is a critical factor in the **initiation** and development of several cancers, including ovarian cancer” (Saed Report, p. 5 (emphasis added)), is not supported by the references cited (Saed et al., 2011; Senthil et al., 2004) that, to the contrary, refer to oxidative stress generated by anticancer agents in malignant ovarian cancers. Saed et al. (2011) and others (e.g., Senthil et al., 2004) have examined markers of oxidative stress in the circulation of ovarian cancer patients but this is a generalized response seen in many cancer patients *after* the development of tumors.

Dr. Saed then goes on to describe studies in which he has examined markers for early detection of ovarian cancer and genetic point mutations (SNPs) in antioxidant enzymes that may govern chemoresistance of EOCs to the chemicals cisplatin and taxotere. He cites his one paper (Fletcher et al., 2016) more than a dozen times throughout the text as showing that “[t]here is now an association of specific SNPs in key oxidant and anti-oxidant enzymes that impact increased **risk** of ovarian cancer” (Saed Report, p. 8). This statement is not supported by his research that examines SNPs induced by chemotherapeutic drugs with no relationship to ovarian cancer risks. Dr. Saed’s misinterpretation of his SNP findings and its lack of relationship to the development of ovarian cancers and his recent talc data are confirmed in his deposition (Saed Dep. Vol. I 201:17-209:4, 211:6-218:24).

In an attempt to link oxidative stress to the process of cancer development, Dr. Saed states, “[t]he oxidative damage to 8-Oxo2- deoxyguanosine, a major product of DNA oxidation, induces genetic alterations in oncogenes and tumor suppressor genes that have been involved in tumor initiation and progression” (Saed Report, pp. 9-10), again referencing Fletcher et al. (2016). In fact, Dr. Saed did not study oxidative damage to this DNA adduct in his cited study.

Talcum powder and increased risk of ovarian cancer (Saed Report, p. 10): This section is filled with inaccuracies in the text and misinterpretation of studies in the peer-reviewed scientific literature by my research group and others. His misstated references are detailed below.

The statement, “In its natural form, some talc contains asbestos” (Saed Report, p. 10) is unreferenced and fails to acknowledge that the deposits from which Johnson’s Baby Powder and Shower to Shower have been sourced over time are not associated with asbestos contamination (Boundy, et al., 1979; Pira, et al., 2017). And ultimately, Dr. Saed testified at his deposition that the presence or absence of asbestos in cosmetic talcum powder products is irrelevant to his opinions (Saed Dep. Vol. I 264:2-5).

His statement that “the carcinogenic effects of asbestos have been extensively studied and documented in the medical literature” references two papers. The first is one by our group (Haegens et al., 2005), in which we did **not** study carcinogenic effects of asbestos. In fact, we studied the development of pulmonary fibrosis, a nonmalignant disease, in mice with the capability to generate oxidants and mice without this capacity in short-term inhalation studies. The other reference he cites, Muscat and Huncharek (2008), also does **not** describe carcinogenic effects of asbestos. This paper is a review concluding that “[m]echanistic, pathology and animal model studies have not found evidence of a carcinogenic effect. In summary, these data collectively do **not** indicate that cosmetic talc causes cancer” (Muscat and Huncharek, 2008). It is unclear why Dr. Saed cites these irrelevant publications.

Dr. Saed attempts to equate talc with asbestos fibers in his statement that “it has been proposed that ground talc, as a foreign body, initiates a similar inflammatory response and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response” (Saed Report, p. 10), again citing the Muscat and Huncharek

(2008) article and also a paper by Ness and Cottreau (1999). In contrast, as just noted, the review by Muscat and Huncharek (2008) concluded that perineal use of cosmetic talc does **not** cause cancer. The review by Ness and Cottreau (1999), entitled “Possible role of ovarian epithelial inflammation in ovarian cancer,” proposes the novel hypothesis that a common mechanism underlying ovarian cancer is inflammation via oxidative stress and cytokines, which may be mutagenic. A subsequent letter by Balkwill (2000) questions this simplistic comment, stating that “it is possible that inflammatory cytokines are important in the evolution of many different malignancies and not just epithelial ovarian cancer.” In essence, Dr. Saed has stolen these ideas as a basis for his emerging scientific research without referencing either of these citations in his recently accepted paper.

Dr. Saed states that “[t]here has been concern about a possible link between talcum powder usage in the genital [area] and ovarian cancer, as well as lung cancer in workers exposed to talc in an occupational setting” (Saed Report, p. 10), citing a paper by Karageogi et al. (2010). This group studied the possible relationship between use of talcum powder and **endometrial** cancer risk, found no statistical association, and concluded that future and larger studies were needed. No references are provided to support Dr. Saed’s statement regarding “lung cancers in workers exposed to talc in an occupational setting” (Saed Report, p. 10). In fact, many cohort studies show the **lack** of mesothelioma development in talc miners and millers (Rubino et al., 1976; Rubino et al., 1979; Coggiola et al., 2003; Gamble and Gibbs, 2008; Addison and McConnell, 2008; Anderson et al., 2017; Boffetta et al., 2018; Garabrant and Pastula, 2018; Pira et al., 2018). These many peer-reviewed papers are not referenced in Dr. Saed’s report.

Dr. Saed states that “[s]tudies that exposed lab animals (rats, mice and hamsters) to asbestos-free talcum powder in various ways have had mixed results, with some showing tumor formation and other finding only inflammation” (Saed Report, p. 10-11), citing only two references. But again, these references do not support his statement. The paper by Graham and Graham (1967) injected a huge amount of **tremolite asbestos (not talc)** into the peritoneum of animals and did not find asbestos fibers in the ovaries after this route of administration. The other reference is an epidemiologic study by Langseth and Kjaerhaim (2004), in which they did not study inflammation by pathology or other measures. This study looked at ovarian cancers in Norwegian pulp and paper workers exposed to asbestos, talc or both dusts. The authors state that “[t]he results do not confirm an association between exposure to asbestos, talc, and total dust and ovarian cancer” (Langseth and Kjaerhaim, 2004, Abstract).

Dr. Saed also misstates the conclusions of the IARC panels in 2010 and 2012 and obviously did not review the many life-time rodent studies showing neither mesothelioma nor ovarian cancer development by exposure to talcs. Moreover, fibrous, non-asbestiform talcs were not classified as human carcinogens by IARC (2010) as Dr. Saed claims.

On page 12 of his report, Dr. Saed states, “The ability of talc particles to migrate through the genital tract to the distal fallopian tube and ovaries is well documented,” citing two references. This statement is **not** supported by the first reference, his Update review (Saed et al., 2017), nor the study referenced (Kunz et al., 1997). These researchers used labeled protein spheres of sperm size that were placed at the entrance of the cervical canal. This artificial means of applying a soluble protein in no way resembles perineal application of talc, and the authors state that “a large proportion of the macro spheres remains at the site of application.” Dr. Saed conceded this error at his deposition. (Saed Dep. Vol. I 322:6-323:20.)

No support is provided for Dr. Saed’s conclusion that migration and accumulation of talc occurs in the ovary. In fact, although he references the IARC (2010) monograph above, he fails to state the conclusions: “[o]n balance, the [w]orking [g]roup believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak...[s]tudies in animals (rodents, langmorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries” (IARC, 2010, p. 411).

On page 12, Dr. Saed also states, “It has been suggested that the associations between perineal talc dusting and ovarian cancer might be explained by the induction of ANTI-MUC1 antibodies.”<sup>57</sup> This reference is to a paper by Cramer et al. (2005) suggesting that talc might affect systemic immunity. Dr. Saed does not reference the subsequent Letters to the Editor by other scientists, including one stating that “the conclusion about genital talc exposure increasing ovarian cancer risk via diminished antibody levels is not supported by their own data...this speculative assumption was ruled out years ago by electron microscopy studies showing no relationship between genital dusting and ovarian talc particle concentrations” (Muscat and Huncharek, 2005).

On page 12, there is also a sentence referencing our peer-reviewed study contrasting gene alterations by crocidolite asbestos and talc in human mesothelial cells and ovarian epithelial cells (see Table 6 above). Dr. Saed does not mention our results showing **no** changes in gene expression in human ovarian cells after exposure to talc, limits his text to our results in mesothelial cells, and states that “the authors found that nonfibrous talc at low concentrations [caused] an increase in the expression of Activating Transcription Factor 3 (ATF3) ...” He does not acknowledge that ATF3 was characterized as an **inhibitor** of inflammation in our studies, and that unlike asbestos, no changes in gene expression were observed at 24 hours in mesothelial or ovarian epithelial cells after exposures to talc. Most importantly, he fails to state that talc changes on cell viability and gene expression were significantly less than those found with asbestos and comparable to negative control dusts not associated with disease causation, i.e., fine titanium dioxide and glass beads.

Dr. Saed does not reference our follow-up study, in which gene expression was compared in both mesothelial and ovarian epithelial cells after exposure to asbestos, talc and control

particles (Hillegass et al., 2010). These studies confirmed that talc-induced gene alterations were quantitatively and qualitatively different from asbestos and comparable to the negative control particles, titanium dioxide and glass beads.

On pages 13-20, Dr. Saed describes recent experiments from his laboratory on ovarian cancer cell lines, macrophages, and ovarian epithelial cells exposed to two cosmetic talcum powders for **24 hours**. For reasons that are unclear, he added four concentrations of talcs diluted and suspended in DMSO (dimethylsulfoxide), a toxic solvent chemical used to solubilize water-insoluble chemicals. It is likely that DMSO coated the surfaces of the talc particles, and changed talc's normal reactivity with cells. He also does not use a positive toxic agent, such as asbestos, or a negative control agent (an inert particle such as glass beads), prerequisites for interpretation of his results. In brief, he measures RNA expression and protein levels of antioxidant/oxidant-related enzymes and a protein marker that can be elevated with the onset of ovarian cancer (CA-125) in cell medium. The data from this study, including results and statistical significance, are not presented in Research Findings (Saed Report, p. 16) although it is stated that "[r]ecent studies from our laboratory have shown **conclusively** that talcum powder alter[s] key redox and inflammatory markers, enhance[s] cell proliferation in EOC cells, which are hallmark of ovarian cancer" (*id.*). Again, Dr. Saed's research update summary (Saed et al., 2017) is referenced repeatedly, but this paper does not present any original data on talc exposures. Statements such as "[c]ollectively, these findings demonstrate that talc treatment induced gene point mutations that happen to correspond to SNPs in locations with functional effects" (Saed Report, p. 19) are not supported by his scientific data as presented here. In attempting to attribute findings of SNPs to treatment with talc, Dr. Saed is trying to make a case for mutations by talc in the causation of ovarian cancer. However, it has been demonstrated historically in many cell types that asbestos fibers are not mutagenic using a number of assays (reviewed in Mossman, 2018). Thus, findings as presented below in his manuscript (Fletcher et al., in press) with talc are unusual and incredible due to the short time frames of talc exposures, i.e., 24 to 72 hours. Moreover, the statement, "In summary, this research clearly demonstrates that talcum powder induces inflammation and alters the redox balance favoring a pro-oxidant state in normal and EOC cells" makes no sense as Dr. Saed did not examine inflammation, an orchestrated response of many cell types, in his short *in vitro* experiments. He also did not measure oxidant release from cells or oxidative stress directly in his cell cultures, important prerequisites for conclusions on the oxidant state of cells.

Dr. Saed's in-press manuscript (Fletcher et al., in press) was apparently shared with other plaintiffs' experts, including Dr. Zelikoff (Zelikoff Dep. 55:3-24). The research and preparation of this manuscript by Dr. Saed was funded by plaintiffs' attorneys. It serves as the sole basis supporting the theory that talcum powder causes oxidative stress, inflammation and ovarian cancer. The paper, in which Dr. Saed claims to describe a "molecular basis" for how talcum powder causes transformation of normal ovarian cells to cancer cells, is severely flawed, and the data it presents are unconvincing. He has not



demonstrated a link between talc and ovarian cancer development. Moreover, he failed to state in his initial submission of the manuscript to *Gynecologic Oncology*, as required by the Conflicts of Interest forms for that journal, that his study is funded by plaintiffs' attorneys and that he has been paid substantially as a consultant for them. Instead, he stated on page 13 of his submission, "The authors have no conflicts of interest to declare." My conclusions on the lack of merit of his findings are supported by the original reviewers who rejected the paper. In reviews of his paper received on 9/19/2018, Reviewer #1 states, "In this reviewer's opinion the cell line studies alone and the increase in CA-125 while intriguing are not sufficiently convincing." Reviewer #1 also states, "The significance of SNP alterations should be further clarified." And most importantly, "The first bulleted highlight, 'Oxidative stress is a key mechanism to the initiation and progression of ovarian cancer' is not supported by this investigation and should be omitted." Reviewer #2 states "their data do not show, despite the authors' claim, any evidence that these cells are transformed. Specifically, no experiments documenting changes in cell survival, proliferation or resistance to apoptosis have been performed. Consequently, neither tumor initiation nor progression is documented in this study as opposed to the statement in Highlight #1 and elsewhere. While changes in redox potential play an important role in tumor biology in general, the present data are insufficient to back up the claim that talcum is central to the development of ovarian cancers. ...The fact that SNPs were changed following such short exposure to talcum is surprising and makes one wonder what the biological effect of such changes may be." It is important to note that the data submitted in this paper were after exposures of cells to talc samples for **48 hours (which Dr. Saed remarkably now claims was a typographical error)** (Saed Dep. Vol. I 185:6-186:7; Saed Dep. Vol. II 487:15-25). This time point is stated several times in the submitted paper, including the Abstract, Methodology, Results and Figure Legends. In conclusion, the editorial decision on this paper was rejection with the editorial comment, "Please note that a revised version of the current manuscript should not be submitted for another review to *Gynecologic Oncology*." Instead of truthfully reporting the substance of the reviewers' comments at his January 23, 2019 deposition, Dr. Saed stated, "[y]eah, they like it, they love my work" (Saed Dep. Vol. I 49:3).

To address the short time frame of exposure questioned above as "surprising," Dr. Saed recently resubmitted his paper to the lower-impact journal *Reproductive Sciences*. In this paper, he supposedly presents data from exposures to talc over a 72-hour period. It should be noted that the same data in Figures 1-4 from the *Gynecologic Oncology* submission at 48 hours are now presented using identical Figure Legends 1-4, with the exception that 48 hours has been changed to 72 hours in each Figure legend and on the ordinate of all graphs. In Figure 1, panels A, C and D are the same as in the previous manuscript, and panel B has been changed. In Figure 2, panels B, C and D are the same as the previous submission, but Panel A is different. In Figure 3, panels C and D are the same, and Panels A and B are different, and Figure 4 is identical, but 48 hours has now been changed to 72 hours in the Figure legend. In summary, Dr. Saed now presents most of his 48-hour data as 72-hour data. This misrepresentation of data is a blatant example of scientific

misconduct. The manuscript was submitted to Dr. Lawrence Layman, an Associate Editor of the journal. Dr. Layman is in the same department and University as Dr. Michael Diamond, a co-author of Dr. Saed's Update/Review article (2017), the principal investigator of Dr. Saed's past research on ovarian cancers, and his former business partner in Dr. Saed's consultant enterprise, DS Biotech (Saed Dep. Vol. I 284:11-285:18). Dr. Saed also reveals in this deposition that he was first retained and paid for this work in 2017 (*id.* 38:13-16). In addition to misrepresenting the time points of his study and the many concerns expressed by reviewers after his submission to *Gynecologic Oncology*, I note other discrepancies in time points of talc exposures between what is reported in his expert report, abstracts (see below) and his two manuscript submissions. It is impossible to assess his research data, which are often not presented as original values. Other graphs present data as a percentage of controls, and statistical significance values are not included on figures, as would be required in most peer-reviewed journals. Instead, Dr. Saed inserts the sentence, "All changes in response to talc treatment were significant ( $p < 0.05$ ) in all cells as compared to controls" on all figures (Fletcher et al., in press, p. 15). He also states in every figure legend that "[e]xperiments were performed in triplicate," when in fact his testimony and notebooks show that this is false (*id.*). There are many flaws in the methodology used. For example, the MTT assay, which measures cell metabolism, is misinterpreted as an assay measuring cell proliferation (Hillegass et al., 2009).

Contrary to instructions for submission of papers to *Reproductive Sciences*, Dr. Saed does not relate his research funding source or disclose his conflicts of interests in this manuscript. Since his studies were funded by plaintiffs' attorneys, these are serious breaches of scientific conduct. Dr. Layman has expedited publication of this paper with Comments to the Author from only one reviewer, who replies in three brief sentences, including the notation that the manuscript is "wordy." Dr. Saed apparently resubmitted the paper that was received with the Comment: "Well done" and acceptance of the paper by Dr. Layman on 1/14/2019. This superficial and expedited review of a submitted paper is very unusual.

I was also asked to review Dr. Saed's laboratory notebook (SAED000001-000097) that he presented for the studies reported in his manuscript. This is not a normal laboratory notebook, which should present daily and sequential entries and information on cell counts, observations, raw data and details on individual experiments. Instead, the notebook lists abbreviated standard methodology (either hand-written or pasted from other documents, cell sources with no details on their growth characteristics or responses to talc by microscopy) and has been "cut and pasted" to include or exclude sample ID numbers from spreadsheets, and final figures from his manuscript before all data were analyzed statistically at the end of the notebook (SAED000093-000097). Data entry was often not in normal sequence and there were often large gaps in time between entries, suggesting that the notebook was put together "after the facts." It was impossible to examine much of the raw data, but Dr. Saed stated during his deposition that only one

sample per individual cell type was examined in each assay and that numbers that appeared to differ from groups were thrown out of the data set. This scientific misconduct was attributed to his technician and a statistician who determined outliers according to his deposition testimony. Especially alarming were the lack of details and statements such as “[c]ells doubled in one day” (SAED000002 (dated Jan. 29, 2018)). Normal ovarian epithelial cells would never double in one day. The method of talc dilution and exposure also makes no sense in that concentrations from 2.5 to 50 microliters (SAED000004 (dated Feb. 2, 2018)) were apparently added to cells in medium. These minute volumes could in no way cover the surfaces of cells in a Petri dish. This suggests that cells were not exposed to talcs.

In conclusion, the statements in Dr. Saed’s “[s]ummary of opinions” (Saed Report, pp. 20-21) are **not supported** by his research results, peer-reviewed studies in the scientific literature or conclusions of panels of scientists. He does not exhibit knowledge of relevant scientific literature, list peer-reviewed papers on mechanisms of cancer development by asbestos, or include references showing the lack of cancer development by talc. He has not published any credible peer-reviewed papers on research from his laboratory in peer-reviewed journals in the fields of toxicology and cancer research, and his data, as recently submitted to *Reproductive Sciences*, are flawed and unrealistic from many standpoints. His manipulation of research data and time points and failure to declare conflicts of interest or bias in the funding of and publication of his research results are serious issues of scientific misconduct that should be brought to the attention of his co-authors and the Editor of *Reproductive Sciences* before his article is published. He alludes to his research data, stating that “the molecular effects resulting from Johnson’s Baby Powder exposure exhibits a clear dose-response pattern,” but does not support this statement and others with his data or references in the peer-reviewed scientific literature. His final opinion that “Johnson’s Baby Powder exposure worsens the prognosis for patients with ovarian cancer” (Saed Report, p. 21) is highly speculative, unfounded and unreferenced.

### **XIII. Scientific Evidence Does Not Support The Hypothesis And Opinions Of Dr. Zelikoff.**

Background and Qualifications: Dr. Zelikoff obtained her Ph.D. in Experimental Pathology and Immunology in 1982 and is a tenured faculty member in Toxicology at the NYU Institute of Environmental Health Sciences.

Methodology: As a general matter, Dr. Zelikoff purports to have followed a rigorous methodology in preparing her report, but many aspects of her approach were not scientific. She relies heavily on expert reports by plaintiffs’ other experts, as well as depositions and internal documents supplied by plaintiffs’ counsel, none of which are legitimate scientific literature and all of which have biased her opinions and conclusions. Indeed, Dr. Zelikoff conceded that she did not attempt to ensure that she was provided with documents that tell the entire story, especially with respect to asbestos testing results (Zelikoff Dep. 275:13-276:20). Although she claims to have performed searches of the scientific literature, many high-impact, peer-reviewed



scientific papers on talc and ovarian/lung cancers are not listed in her Materials and Data Considered or referenced in the text of her report. Others are listed but not described accurately. A review of Materials and Data Considered shows that she also relies heavily upon abstracts, opinion papers and book chapters that are not peer-reviewed. Finally, several of her statements were cut and pasted from the reports of other experts or the Internet without citation, further calling into question the reliability of her statements (*see* Zelikoff Dep. 75:10-124:15).

Dr. Zelikoff claims that her opinions only concern biological plausibility, not causation (Zelikoff Dep. 72:23-73:16, 130:22-131:12). She emphasizes that, for her opinions, “[b]iological plausibility does not mean proof of mechanism” (Zelikoff Report, p. 2). Dr. Zelikoff has indeed not supplied proof of a mechanism through which talc use causes ovarian cancer. The issues discussed in this section demonstrate the serious methodological deficiencies in her attempt to posit that a mechanism is even plausible. In fact, each section of her report contains numerous errors in her text, references and interpretation of results that undermine her credibility and conclusions.

Talc, Asbestos and Heavy Metals (Zelikoff Report, pp. 3-12). Dr. Zelikoff’s discussion of fibrous talc, asbestos and other alleged talc contaminants demonstrates a misunderstanding of fundamental concepts of minerology and inaccurately presents the data regarding whether cosmetic talc products are contaminated and/or unsafe due to the alleged contamination.

In her discussion of Fibrous Talc (Zelikoff Report, p. 4), Dr. Zelikoff, like Dr. Saed, misstates the conclusions of the 2010 and 2012 IARC panels in her statement that “[i]n its fibrous form, talc has been classified as a Group I, known carcinogen.” In fact, only talc containing asbestos or asbestiform fibers was considered to be a Group 1 carcinogen (IARC, 2012); fibrous, non-asbestiform-containing talcs were not (IARC, 2010). Dr. Zelikoff repeatedly confuses fibrous talc with talc containing asbestos. Fibrous talcs do not induce tumors in animals (Smith et al., 1979; Stanton et al., 1981), nor pre-malignant changes in rodent epithelial and mesothelial cells (Wylie et al., 1997), as explained in peer-reviewed literature that was not cited by Dr. Zelikoff. She also fails to reference studies by Wagner (Wagner et al., 1975; Wagner et al., 1980) and others, which show that talc does not produce mesotheliomas or lung malignancies after administration to animals by a variety of routes.

Dr. Zelikoff’s discussions of Asbestos and Asbestos in Talc (Zelikoff Report, pp. 5-8) contain numerous mistakes. Dr. Zelikoff does not claim to be an expert in asbestos or minerology (Zelikoff Report, pp. 1-2; Zelikoff Dep. 162:20-164:24). This is evident throughout many sections of her report where Dr. Zelikoff equates nonasbestos amphiboles and serpentine fibers with asbestos and fails to differentiate between asbestiform and non-asbestiform fibers. Moreover, the studies Dr. Zelikoff cites in attempting to show that “the presence of asbestos in cosmetic talc has been reported in the literature” (Zelikoff Report, p. 6 (citing Rohl et al., 1976, Paoletti et al., 1984, and Cralley et al., 1968)) have been questioned by other scientists and panels. For example, Dr. Zelikoff fails to cite a response by Krause and Ashton (1978) questioning

misidentification of asbestos in the Rohl et al. (1976) study. The IARC 2010 panel reached similar conclusions regarding these three papers, noting, among other things, that no data were provided to support the statement that “some [fibers] may have been anthophyllite, tremolite, pyrophyllite or chrysotile” in the Cralley et al. (1968) study, and that “no information was provided on the concentration of minerals, including tremolite and quartz” in the Paoletti et al. (1984) study (IARC, 2010, pp. 303-305). Finally, in arguing that a single fiber of asbestos or talc would supply a plausible biological mechanism (a theory that has been consistently rejected in the scientific community), Dr. Zelikoff misquotes a deposition by Robert Glenn, whom she describes as “[t]he former Director of National Institute for Occupational Safety and Health (NIOSH).” Mr. Glenn was never the Director of NIOSH. Moreover, Dr. Zelikoff conceded that she did not fully read Mr. Glenn’s deposition and failed to cite his statements that talc is not genotoxic or mutagenic (Zelikoff Dep. 548:20-549:8).

In her section on Heavy Metals (Zelikoff Report, pp. 8-12), Dr. Zelikoff describes three heavy metals: nickel, chromium and cobalt, which have been classified as carcinogens or probably carcinogens by IARC panels, but again misrepresents the scientific data. Specifically, she references the Cralley et al. (1968) paper (which, as noted above, was discounted by the IARC 2010 panel) in support of the statement that “[s]tudies here suggest that women who used talcum powder in the 1960s could have been exposed to considerable amounts of toxic heavy metals depending on the type of talc used and frequency of use” (Zelikoff Report, p. 10). However, in these and other studies cited, heavy metals were found in miniscule amounts (parts per million) or found at “levels to be within safe limits” in talcum powders purchased off the shelf (*id.*, p. 11). Dr. Zelikoff also concurs with the expert report of another plaintiffs’ witness, Dr. Michael Crowley, who “concludes that fragrance chemicals may contribute to the inflammatory response, toxicity and potential carcinogenicity of Johnson & Johnson’s talcum powder products” (Zelikoff Report, p. 12). This statement is flawed from many standpoints, most notably that the trace chemicals Dr. Crowley lists have not been shown to be carcinogens in humans or animals, even at high amounts. In any event, Dr. Zelikoff conceded that none of the studies she cites in support of her theories regarding heavy metals and fragrances have to do with ovarian cancer or inflammation in the ovaries (Zelikoff Dep. 281:1-282:8; 291:14-24; 313:21-314:14). Nor did she compare whether the amounts of metals at issue in the studies she cites are similar to the doses women would be exposed to from metals allegedly present in cosmetic talc products (*id.* 295:12-17).

Exposure – Talc Particle Access to the Body (Zelikoff Report, pp. 12-17). Dr. Zelikoff’s opinions regarding talc exposure routes – including that “[a]nimal and human studies demonstrate that talcum powder products can migrate from the perineal region to the ovaries” (*id.*, p. 14) and that “[t]here is substantial evidence in the scientific and medical literature that support a conclusion that talc powder particles can reach the ovaries through inhalation” (*id.*, p. 17) – are also not supported by the scientific data.

On pages 12 to 17, Dr. Zelikoff speculates that talc can migrate upwards through the female reproductive tract, i.e., retrograde migration. In support, she cites a series of studies performed decades ago where boluses of talc were applied intravaginally or within the uterus, **not** externally to the perineum. She acknowledged, however, that there are no studies showing that talc applied externally (i.e., to the perineum) migrates to the ovaries (Zelikoff Dep. 339:21-340:14). Dr. Zelikoff attempts to bolster her opinion with limited studies in humans including a case report demonstrating the presence of talc particles in the pelvic lymph nodes of a woman with ovarian cancer (Cramer, 2007). But a single case report is not strong scientific evidence, and there could be other explanations for this finding. In any event, the same body of literature Dr. Zelikoff relies on was examined by the IARC 2010 panel, which concluded: “[o]n balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak...[s]tudies in animals (rodents, langmorphs and non-human primates) showed no evident of retrograde transport of talc to the ovaries” (IARC, 2010, p. 411). As IARC further observed, the positive findings in some studies in humans, such as after surgical procedures, “may be confounded by the various levels of dysfunction in clearance from the female reproductive tract due to underlying pathologies” (*id.*).

Pages 14-15 of Dr. Zelikoff’s report summarize the results of inhalation studies showing that fine and ultrafine particles of a variety of types are inhaled and have been detected at distal sites in the body. After inhalation by animals, very small particles can enter the blood stream or lymphatic channels to accumulate in regional lymph nodes, as has been shown in the general population (Dodson et al., 2000). However, as Dr. Zelikoff conceded, there are **no** peer-reviewed studies demonstrating that inhaled talc causes inflammation in the ovaries (Zelikoff Dep. 302:2-303:10).

Mechanisms of Cancer (Zelikoff Report, pp. 17-21). Dr. Zelikoff’s general discussion of cancer mechanisms also contains a number of inaccuracies and incorrect assumptions, demonstrating that her methodology was not rigorous or sound.

Dr. Zelikoff’s discussion overlooks that there are multiple histological subtypes of ovarian cancer, all of which are likely not caused by the same mechanism. Dr. Zelikoff conceded that she did not analyze the biological plausibility of ovarian cancer by subtype of ovarian cancer, and offered no opinion as to whether the subtypes have the same etiology (Zelikoff Dep. 193:11-195:7).

Dr. Zelikoff also omitted crucial data and incorrectly presented other data. On pages 17-19, Dr. Zelikoff provides an overview of the cancer process, emphasizing the importance of genetic mutations by genotoxic carcinogens. However, she fails to acknowledge a critical peer-reviewed paper showing that talc particles from three different mining sites in Europe, including Italian, Spanish and French talcs, were **not** genotoxic to mesothelial cells. In contrast, both chrysotile and crocidolite asbestos induced markers of DNA damage (Endo-Capron et al., 1996). Similarly, on page 19, Dr. Zelikoff concludes that “Reducing immunity to MUC1 could be one mechanism by which talc increases endometrial and/or ovarian cancer risk” (Zelikoff Report, p. 19 (citing Karageori et al.,

2010)). But Karageorgi et al. (2010) studied the possible relationship between use of talcum powder and **endometrial** (not ovarian) cancer risk, found no statistical association, and concluded that future and larger studies were needed.

Dr. Zelikoff's description of the processes of acute and chronic inflammation on pages 19-21 fails to acknowledge that talc (unlike cigarette smoke and asbestos) is not associated with chronic inflammation or tumors in the lung, pleura or elsewhere. As summarized by the IARC 2010 panel, "[t]alc is cytotoxic to macrophages and may be able to induce fibrosis and chronic inflammation in animals [after large injections]. However, the macrophage response to talc appears to be weaker than for other fibrogenic dusts such as quartz" (IARC, 2010, p. 398). As summarized in **Section VI. D** above, chronic inflammation by asbestos, silica and cigarette smoke may lead to cancers, but this should not be confused with the nonmalignant disease pulmonary fibrosis. We have known for decades that chronic inflammation fosters growth and angiogenesis of malignant tumors of a variety of types. However, talc's theorized action as a chronic inflammatory agent producing excessive oxidants in the initiation or development of ovarian cancer is highly speculative and illogical when considering the many properties of talc particles that render it inert and dissimilar to asbestos, silica or cigarette smoke.

Finally, several other statements by Dr. Zelikoff in her description of Ovarian Cancer and Inflammation (Zelikoff Report, pp. 20-21) are unsupported by her references. For example, she states that "[r]ecent clinical and prospective data suggest that C-reactive protein (CRP), a marker of global inflammation, is associated with increased ovarian cancer risk" (Zelikoff Report, p. 20 (citing Li, 2017; Poole, 2013; Jing, 2017)). Poole and colleagues measured three plasma markers of inflammation (CRP, IL-6 and TNFaR2) in prospectively collected samples from the Nurses' Health Study I and II and the Women's Health Study, all of which found no link between talc usage and risk of ovarian cancer (Gertig et al., 2000; Gates et al., 2010; Houghton et al., 2014). Indeed, Poole found no significant associations between IL-6 or TNFaR2 protein expression and ovarian cancers, observations refuting Dr. Zelikoff's hypotheses that these are important inflammatory mediators in the causation of talc-induced inflammation and cancer (Zelikoff Report, pp. 21-24). Moreover, Dr. Zelikoff makes numerous errors in citing a study by Wu et al. (2009) on page 21. First, she omits that a major purpose of the Wu study was to examine the effect of NSAIDs on incidence of ovarian cancer, and that it found that ovarian cancer incidence did not decrease with increasing frequency and years of NSAID use – which is highly inconsistent with the inflammation theory (Zelikoff Dep. 471:20-474:4). Second, she ignores that the paper by Wu and colleagues was a very small study in LA County involving approximately 600 patients diagnosed with ovarian cancer, and that the authors discuss the many limitations and inconsistencies in their studies and other patient studies in the literature.

Mechanisms of Inflammation (Zelikoff Report, pp. 21-27). This section is replete with instances in which Dr. Zelikoff contradicts fundamental elements of cellular biology, incorrectly characterizes the scientific data and speculates.

Dr. Zelikoff's conclusions regarding inflammation do not take into account the fact that talcum powder is used as an **anti-inflammatory** agent in applications to the dermis of the genital area such as diapering. In fact, there are **no** human studies suggesting that talc causes inflammation in the female reproductive tract. Dr. Zelikoff's conclusion that a "talcum powder-induced [inflammatory] cascade provides significant biologic and toxicologic support for a conclusion that talcum powder products can cause ovarian cancer" (Zelikoff Report, p. 26) is unfounded and not supported by peer-reviewed scientific data.

In the introduction to this section, Dr. Zelikoff incorrectly cites several studies. First, the review by Maccio and Madeddu (2012) (cited in Zelikoff Report, p. 21) addresses the importance of proinflammatory cytokines on "promoting ovarian tumorigenesis and cancer progression," as well as the risk of ovarian cancer to incessant ovulation, but does not discuss or mention talc as an inflammatory or cancer-causing agent. In addition, on page 22, Dr. Zelikoff cites an outdated review (Ness and Cottreau, 1999) entitled "Possible role of ovarian epithelial inflammation in ovarian cancer." Those authors' conclusions were subsequently questioned by Balkwill (2000), who stated that "inflammatory cytokines in the tumor microenvironment might not contribute to genetic damage initiating cancer, but could be a fuel that promotes the cancer process." This argues against a role of talc in initiating ovarian cancers, as it does not cause damage to DNA, genetic damage or chronic inflammation. A more recent review, Landen et al. (2008), which Dr. Zelikoff fails to cite, presents a model of ovarian cancer that incorporates the roles of tumor cell mutations and the host microenvironment in initiation and development of tumors. This model precludes a role of talc in initiation and progression of ovarian cancers, as talc does not cause genotoxic changes or mutations in cells (Muscat and Huncharek, 2008; Endo-Capron et al., 1993; EPA, 1992; IARC, 2010).

Dr. Zelikoff's sections on Cytokine Networks and Macrophages (Zelikoff Report, pp. 22-24) contain numerous errors. The talc uptake by macrophages that has been shown in studies is most likely related to normal defense mechanisms. Moreover, Dr. Zelikoff's comparisons between fine and nanoscale talc are unjustified, since nanoscale talc would be a miniscule fraction, if any occurred in cosmetic talc (Zazenski et al., 1995). And although it is well documented in the nanotoxicology field that nano-sized materials of a variety of types are more toxic to cells than fine, larger particles, it is highly speculative to link toxicity as manifested by cell injury and death (problematic in *in vitro* studies using massive concentrations of talc, as in Dr. Saed's experiment) to mechanisms of cancer induction. Simplistically, dead cells or injured cells that cannot divide cannot give rise to premalignant or malignant cells. Dr. Zelikoff's comparisons between plasma concentrations of cytokines in ovarian cancer patients (Poole et al., 2013; Trabert et al.,



2014) and levels in cells or animals exposed to talcs are unjustified.

Dr. Zelikoff's discussion of Macrophages (Zelikoff Report, p. 22-23) also severely mischaracterizes our Shukla et al. (2009) study. Specifically, Dr. Zelikoff fails to mention that we examined gene expression in human ovarian epithelial cells, in addition to mesothelial cells. These and additional data were examined subsequently by Hillegass et al. (2010) to show that effects of talc were comparable to those shown with the negative control particles, fine titanium dioxide and glass beads. She also misinterprets our data on Activating Transcription Factor (ATF3), the only gene upregulated at an early time point at low concentrations of talc in mesothelial cells. Dr. Zelikoff states that ATF "modulates production of pro-inflammatory cytokines and growth factors in human lung cells" (Zelikoff Report, p. 23), but fails to mention that it is a **negative** regulator of these inflammatory proteins. We also stated that "our experiments suggest that human mesothelial cells adapt to or undergo repair after exposure to [talc]" (Shukla et al., 2009). Finally, Dr. Zelikoff's subsequent statement that talc "caused increased expression of transcription factors associated with the inflammatory process in a **time** and dose-dependent manner" (Zelikoff Report, p. 26 (emphasis added) (citing Shukla et al., 2009)) is incorrect.

The discussion on Talc-Induced Inflammation and Oxidative Stress (Zelikoff Report, pp. 25-26) likewise contains a number of inaccuracies and citation errors. Basic principles of toxicology and the importance of dose-response relationships are ignored in Dr. Zelikoff's initial statement that "[e]ven a single dose of a carcinogen can produce effects that are adverse to cells and tissue at the site of exposure" (Zelikoff Report, p. 25). This statement also ignores the fundamental tenet that injury and repair occur at low or single applications of cancer-causing agents. It is highly problematic that Dr. Zelikoff completely failed to consider the dose threshold needed to trigger the inflammatory mechanism around which her opinions center. Dr. Zelikoff acknowledged that dose contributes to the toxicity and carcinogenicity of an agent (Zelikoff Dep. 262:6-15; 343:10-17), but could not identify the threshold dose of talc necessary to start the biologic process for ovarian cancer (*id.* 263:14-266:15). Her unsupported opinion that a single particle of talc could trigger inflammation leading to ovarian cancer (*id.* 370:8-372:11, 373:16-22, 439:14-441:18) ignores the importance of dose, as does her reliance on studies where animals or cells were exposed to artificially huge amounts of talc that are nothing like the exposures in perineal talc use.

Among other citation issues in this section is Dr. Zelikoff's summary of the Buz'Zard and Lau (2007) study. She cites this publication to illustrate "a well-established methodology called a neoplastic cell transformation assay" (Zelikoff Report, p. 25). However, Dr. Zelikoff neglects to mention that the assay she describes measures lack of contact growth of cells in culture, whereas cells must be injected into animals to ascertain whether they are cancerous. In fact, the neoplastic transformation data presented in Figure 2 (Buz'Zard and Lau, 2007, p. 581) shows that 2 to 9% of the two supposedly

“normal” ovarian cell lines (controls not exposed to talc) in their experiments grew in soft agar suspension. Thus, these cells were already neoplastically transformed, since, as Dr. Zelikoff correctly observes, “non-neoplastically-transformed cells cannot grow in suspension” (Zelikoff Report, p. 25). Moreover, as demonstrated throughout the Buz’Zard study, the supposed talc effects were neither dose-related nor consistent in each cell type. More importantly, the authors did not use proper positive (asbestos) or negative (inert particle) controls in their experiments, as would be necessary to draw conclusions about talc effects.

Dr. Zelikoff’s heavy reliance on the Buz’Zard study is problematic for additional reasons related to that paper’s own improper citation of studies. First, it cites to Van Dyke et al. (2003) (which Dr. Zelikoff includes in her list of materials considered but does not directly cite). But the Van Dyke study stated that links between these short term-*in vitro* assays, chronic inflammation and cancer induction by talc are not justified – undercutting the notion that the Buz’Zard study can support inflammation as a mechanism for talc causing ovarian cancer. Specifically, these authors stated in describing their *in vitro* model: “If macrophages are exposed to particles *in vivo*, a totally different scenario occurs... Certainly one would not observe chronic inflammation which by definition takes weeks to occur inside an animal” (Van Dyke et al., 2003, p. 119). Their study also showed that superoxide (oxidant) release by talc from macrophages is minimal when compared to surface active minerals such as bentonite. Second, the Buz’Zard study discusses a paper by Dr. Zelikoff’s former colleague at NYU, Dr. Kevin Driscoll. In citing the Driscoll study, the Buz’Zard authors state: “[i]n an *in vitro* study of rat cells, both macrophages and neutrophils were found to be mutagenic in response to alpha-quartz dust, talc and diesel soot; however, neutrophils appeared to have a greater mutagenic effect” (Buz’Zard and Lau, 2007, p. 585 (citing Driscoll et al., 1997)). This study is misquoted, as Dr. Driscoll examined alpha-quartz, carbon black and titanium dioxide and **not talc** in these studies.

Dr. Zelikoff’s claim that a study by Keskin et al. (2009) supports “a plausible mechanism for talcum powder-induced ovarian cancer” (Zelikoff Report, p. 25) further shows that she was not careful in reviewing and drawing conclusions from the scientific data. In this chronic study, a bolus of talc was applied daily either intravaginally or to the perineal area of rats for three months. The authors concluded: “[t]alc has unfavorable effects on the female genital system. However, this effect is in the form of foreign body reaction and infections, **rather than being neoplastic**” (Keskin et al., 2009, p. 925, Abstract). They also stated: “Even asbestiform talc is not as carcinogenic as asbestos owing to its chemical and physical properties” (Keskin et al., 2009, p. 926).

Dr. Zelikoff primarily relies on two non-peer-reviewed abstracts by Dr. Saed’s laboratory (Zelikoff Report, pp. 25-26 (citing Fletcher, 2018, and Harper and Saed, 2018)) to support her opinion that the cosmetic talc products at issue cause oxidative stress, inflammation and ovarian cancers. Notably, neither of these abstracts is discussed or

referenced in Dr. Saed's expert report. And neither discloses its sources of materials, funding of the research or conflicts of interest.

It is a significant stretch for Dr. Zelikoff to contend that the sparse content of these abstracts supports her opinions. Specifically, the Fletcher and Saed (2018) abstract claims to have exposed four ovarian cancer cell lines (EOC) and normal ovarian cells to huge amounts of talc (**200** and **500** micrograms/per ml medium) for 24, 48 or 72 hours. They note increases in pro-oxidant and decreases in anti-oxidant gene expression at 24 hours, as might be predicted with any toxic particle exposure, but no statistical analysis is presented to substantiate the "marked" changes they describe or whether these changes increase or decrease with time. The lack of positive and negative control particles, viability assays, and direct measurements of oxidative stress in cells makes these data virtually uninterpretable. It should also be emphasized that these studies are only measuring the mRNA levels, and not proteins or enzyme activities necessary to draw conclusions. Similar concerns preclude interpretation of the findings of the Harper and Saed (2018) abstract. Here, they claim to examine gene point mutations in key oxidant enzymes after exposures to talc (**100** micrograms per ml medium) for 48 hours in both ovarian cancer cells and normal ovarian epithelial cells. They also examine enzyme activities. They list a statistical method in the Methods, but do not present statistical significance values in their table of results. This study's raw data, as well as verification of results by statistical analyses (not to mention its origin and source of funding) should be scrutinized before drawing any conclusions from it. Dr. Zelikoff could not possibly have done her analysis based on these abstracts alone.

Finally, Dr. Zelikoff's narrative regarding Iron-Facilitated Inflammation attempts to make a case for iron in the generation of talc-induced oxidative stress and inflammation, citing studies by Ghio et al (Ghio et al., 1992; Ghio et al., 2012). Those studies measured disturbances of iron metabolism in mesothelial cells in response to 100 micrograms/ml talc, characterizing that dose as "massive" (Ghio, 2012, p. 80, Abstract). Dr. Zelikoff fails to mention subsequent studies by Ghio et al. (2016) that demonstrated that "exposure of cells to **all** particulate matter, including air pollution particles," causes a disruption in iron metabolism in various cell types (Ghio et al., 2016 (emphasis added)). Many materials causing these changes are not carcinogenic.

Summary of Opinions (Zelikoff Report, pp. 27-28). As explained above, Dr. Zelikoff's conclusions are **not** supported by peer-reviewed scientific papers in the literature or basic tenets of toxicology and carcinogenesis. Conclusion #1 is based solely on her examination of reports by plaintiffs' experts claiming that there are carcinogens such as asbestos, heavy metals and fragrance chemicals in cosmetic talc. Conclusion #2 – that talc reaches the ovaries to cause cancer – is also not supported by peer-reviewed scientific literature or panels of scientists. Conclusion #3, claiming that talc causes changes in cell signaling, gene alterations and/or mutations, is contrary to published studies from our and other laboratories. No support exists for the opinion that talc causes

“[n]eoplastic transformation and proliferation” (*id.*, p. 28) in ovarian or other cell types. Moreover, her linking of talc to “[i]nhibition of apoptosis” (*id.*, p. 27) is contrary to published studies showing that talc induces apoptosis, i.e., programmed cell death, in human malignant mesothelioma cells without affecting normal mesothelial cells of the pleura (Nasreen et al., 2000). The sheer number of instances in which the actual reported data do not support Dr. Zelikoff’s opinions is strong evidence that she did not reliably consider the scientific evidence she claims to rely on and that her opinions are unscientific and speculative.

#### **XIV. Conclusions**

- 1) Drs. Saed and Zelikoff both betray a fundamental misunderstanding of the makeup of talc versus asbestos and the peer-reviewed and published research on ovarian cancer.
- 2) None of their opinions is supported by peer-reviewed published scientific research.
- 3) Based on Dr. Saed’s plaintiff-funded research, plaintiffs’ experts propose that talc causes a “pro-oxidant” state in ovarian epithelial cells that then causes chronic inflammation and tumor development. As emphasized above, no conclusions can be drawn about the importance of oxidative stress at the massive concentrations of talc used in the Saed studies. In addition, talcs were added to cultures in a toxic solvent, and proper positive and negative control minerals were not employed. In fact, the responses reported are seen at high exposures to a variety of non-disease-causing agents.
- 4) Contrary to statements in the text, Dr. Saed’s *in vitro* cell cultures cannot measure inflammation, which is an orchestrated response of many cell types of the immune system to foreign matter. He did not measure oxidative stress, inflammation (which takes months or years to develop) or cell proliferation directly in his experiments.
- 5) Neither chronic inflammation nor tumors are observed in long-term, follow-up studies on patients after talc pleurodesis, providing further evidence that chronic inflammation by talc is not linked to cancer development.
- 6) Dr. Zelikoff does not understand the difference among various asbestos types or the differences between asbestos and cleavage fragments.
- 7) There is no scientifically plausible pathway of migration to the ovary or oviducts or fallopian tubes by cosmetic talc particles. Since the IARC 2010 panel’s conclusions stating that there were no scientific studies supporting the phenomenon of retrograde talc movement from the perineal region to the oviducts and ovary, no new studies have demonstrated the existence of a putative pathway or mechanism for the transport of talc in this manner.
- 8) Dr. Saed’s and Dr. Zelikoff’s inflammation theories ignore – and are rebutted by – the available scientific research about talc and about the development of ovarian cancer. Although chronic inflammation may play a role in development of some tumor types, it has not been shown to play a role in ovarian cancer. To the contrary, pelvic inflammatory

disease (PID) and chronic tubal injury or inflammation are not significant risk factors for ovarian cancer (Rasmussen et al., 2016; Malmberg et al., 2016; Zhou et al., 2017). Moreover, evidence regarding any association between aspirin use and anti-inflammatory drugs with reduced risk of ovarian cancer is inconclusive (Ni et al., 2012). In sum, the relevance of chronic inflammation to the establishment of ovarian tumors is far from established.

## **XV. Glossary Of Terms And Abbreviations:**

**Amosite:** a type of asbestos in the amphibole group

**Amphibole:** a broad term for a group of chain silicate mineral with a double chain structure

**Angiogenesis:** development of blood vessels

**Anthophyllite:** a type of asbestos in the amphibole group

**Apoptosis:** programmed cell death

**Asbestiform:** a subset of fibrous minerals implying long fiber length and small fiber thickness

**Asbestos:** a commercial term applied to the asbestiform varieties of serpentine (chrysotile) and amphibole asbestos types

**Asbestosis:** a nonmalignant disease of the lung associated with asbestos exposures

**Bolus:** a large amount or growth

**Carcinogen:** a cancer-causing agent

**Carcinoma:** epithelial cell tumor

**Co-carcinogen:** an agent interacting with a known cancer-causing agent to facilitate the development of cancers

**Chrysotile:** an asbestiform serpentine variety of asbestos

**Cleavage:** the property of a crystal to fracture or break along certain planes

**Crocidolite:** a type of asbestos in the amphibole group

**Cytokines:** proteins that are produced from cells to favor inflammation or disease

**DNA:** deoxyribonucleic acid capable of directing its own synthesis

**Dysplasia:** abnormal tissue development

**EOC:** epithelial ovarian cancer cells

**Epidemiology:** the study of human populations

**Epigenetic:** occurring by processes not affecting the DNA structure

**Extracellular:** outside the cell



**Fibrosis:** the formation of fibrous tissue, usually as a reparative or reactive process

**Genotoxicity:** property of an agent for altering the genome of cells resulting in cell death or altered function and division of cells

**IARC:** International Agency for Research on Cancer

**Inflammation:** a fundamental pathologic process consisting of a dynamic complex in response to an injury or abnormal stimulation

**Intracellular:** within the cell

**In vitro:** maintenance of cells or tissues outside of the body

**In vivo:** in the body

**Macrophages:** cells of the immune system with phagocytic functions

**Mesothelioma:** tumors arising from mesothelial cells

**Metaplasia:** altered cell function

**Mutation:** a heritable alteration in the DNA

**Neoplasm:** a new growth that is benign or malignant

**Neutrophils:** cells of the immune system that originate in the bone marrow or at other sites and are released into the circulation

**NIH:** National Institutes of Health

**Nucleus:** an organelle of the cell containing the genetic material

**Pathology:** the study of disease

**Pathogenesis:** the processes

**Phagocytosis:** process of elimination by cell uptake

**Pleura:** membranes enveloping the lungs and lining the walls of the chest cavity

**Pleurodesis:** a therapeutic process where talc is injected to seal the pleura

**RNS:** reactive nitrogen species

**ROS:** reactive oxygen species

**Talc:** a mineral species that is a 2:1 layer silicate

**Talcosis:** a fibrotic, noncancerous disease of the lung associated with heavy talc exposures in the workplace

**Threshold:** the point at which a stimulus is just strong enough to be perceived or produce a response

**Toxicity:** adverse effects by noxious or poisonous substances

**Toxicology:** the study of toxic substances

**Tremolite:** a type of asbestos in the amphibole group

# EXHIBIT A

**Dr. Brooke Mossman**  
**Prior Deposition and Trial Testimony**

<b>Date</b>	<b>Case</b>	<b>Type</b>
	Case Sealed by Court (Minnesota)	Deposition
July 15, 2014	<i>Fishbain v. Colgate-Palmolive Co., et al.</i> , Case No. MID-L-5633-13AS (Superior Ct. of NJ)	Deposition
Mar. 12, 2015	<i>Winkel v. Calaveras Asbestos, Ltd, et al.</i> , Case No. BC549253 <i>Whitted-Justice v. Colgate-Palmolive Co., et al.</i> , Case No. 5:13-CV-00622-D (E.D.N.C.) (CA Super. Ct.)	Deposition
Aug. 21, 2015	<i>Goldsmith, et al. v. ACandS, Inc., et al.</i> , Consolidated Case No. 24X11000783 (Baltimore Circuit Ct.)	Deposition
Sept. 2, 2015	<i>Goodrich Corp. v. AG Securitas, et al.</i> , Case No. 2008-08-5847 Ohio (Court of Common Pleas)	Deposition
Jan. 22, 2016	<i>Owens v. American Truetzschler, Inc., et al.</i> , Case No. 2014-CP-30-772 (SC Court of Common Pleas)	Deposition
Apr. 6, 2016	<i>Alfaro v. American Talc Co. et al.</i> , Case No. BC583520 (CA Super. Ct.)	Deposition
June 15, 2016	<i>Nosse v. Arvinmeritor, Inc., et al.</i> , Case No. BC603354 (CA Super. Ct.)	Deposition
June 16-17, 2016	<i>Alfaro v. American Talc Co. et al.</i> , Case No. BC583520 (CA Super. Ct.)	Trial
June 22, 2016	<i>LaMonica v. Colgate-Palmolive, et al.</i> , Case No. BC604809 (CA Super. Ct.)	Deposition
July 15, 2016	<i>Nosse v. Arvinmeritor, Inc., et al.</i> , Case No. BC603354 (CA Super. Ct.)	Trial
July 18, 2016	<i>Polakow et al. v. Brenntag North America, Inc., et al</i> Case No: BC599542 (CA Super. Ct.)	Deposition
August 26, 2016	<i>Depoian and Depoian v American International Industries, Inc., et al</i> J.C.C.P. No. 4674 (CA Super. Ct.)	Deposition

Sept 16, 2016	<i>LaMonica v. Colgate-Palmolive, et al.</i> , Case No. BC604809 (CA. Super. Ct.)	Trial
Sept. 26, 2016	<i>B.Jackson v. Colgate-Palmolive</i> Case No. 1:15-CV-01066 (US District Court of Columbia)	Deposition
Sept. 30, 2016	<i>Depoian and Depoian v American International Industries, Inc.</i> J.C.C.P. No. 4674, (CA Super. Ct.)	Trial
Oct. 2, 2016	<i>A Blount v. Colgate Palmolive, et al.</i> Case # BC617806 (CA Super. Ct.)	Deposition
Oct. 11, 2016	<i>All Asbestos Litigation Filed by Gori, Julian &amp; Assoc PC</i> Case No: 14-L-999002 (3 <sup>rd</sup> Circuit Madison, IL)	Deposition
Nov. 21-22, 2016	<i>A Blount v. Colgate Palmolive, et al.</i> Case # BC617806 (CA Super Ct.)	Trial
Nov. 29, 2016	<i>M Lyons, v. Metropolitan Life Insurance Co, et al.</i> , Case No. CGC16276495 (San Francisco Super Ct.)	Deposition
April 5, 2017	<i>S Foster v. Cyprus Amex Mineral Company, et al.</i> , Case No. RG15764371 (CA Superior Ct.)	Deposition
April 17, 2017	<i>D Greene v. ACandS, Inc., et.al.</i> Case No. 24X15000563 (Circuit Ct. Baltimore, MD)  <i>E Link v. ACandS, Inc., et.al.</i> Case No. 24X15000557 (Circuit Ct. Baltimore, MD)	Deposition
May 12, 2017	<i>B Humphrey v. Akzo Nobel Paints, f/k/a Glidden Co., et al.</i> Case No. 16 L 45 (6 <sup>th</sup> Judicial Circuit Ct., Macon County, GA)	Deposition
July 10, 2017	<i>S Hanson v. Colgate-Palmolive Company, et al.</i> Case No: 2:16-cv-34 (US District Ct. GA, Brunswick Div.)	Deposition
July 14, 2017	<i>C Schoeniger v. Colgate-Palmolive Company, et al.</i> Docket No: MID-L-5869-1AS and <i>L Bartlow v. Colgate-Palmolive Company, et al.</i> Docket No: MID-L-5358-16AS, (Superior Court of NJ, Law Division Middlesex County)	Deposition



August 11, 2017	<i>B Wittman, and J Wittman, v Brenntag North America, etc. et. al.</i> Case No: BC646439., (CA Super. Ct. for the County of Los Angeles)	Deposition
August 30, 2017	<i>T Herford and D Herford, Plaintiffs v. AT&amp;T Corp., et al.</i> Case No: BC646315, (CA Super. Ct. for the County of Los Angeles)	Deposition
August 31 & September 14, 2017	<i>R Booker and C Booker, v. Cyprus Amex Mineral Company, et al.</i> Case No: RG15796166, (CA Super. Ct. for the County of Alameda)	Deposition
September 18, 2017	<i>S Jenkins v Avon Products, Inc., et al.</i> Case No: JCCP4674/ 37-2016-00025572, (CA Super. Ct, San Diego)	Deposition
September 19, 2017	<i>RA Stevenson and R Stevenson v MCIC et al.</i> Case No: 24-X-87048500 (Circuit Ct. for Baltimore City, MD)	Deposition
October 10, 2017	<i>D Chapp v Colgate Palmolive et al</i> Case No: 15-CV_____ Case Code: 30100 (Circuit Ct. for Milwaukee County, WI)	Deposition
October 13, 2017	<i>R Abeyta v A&amp;A Building Material Co.,</i> Case No: BC598586 (Superior Court of California, County of Los Angeles)	Deposition
December 19, 2017	<i>J Brooke v Honeywell International Inc.,</i> Case No: 16-2-21021-0 SEA (Superior Court of Washington for King County)	Deposition
January 10, 2018	<i>J Ratcliff v BorgWarner Morse Tec LLC, et al.,</i> Case No: 16-2-18128-7 SEA (Superior Court of Washington for King County)	Deposition
February 19, 2018	<i>J Minneci Estate v Johnson &amp; Johnson, et al.,</i> Case No: 2017-CA-000999-O (Circuit Court of the 9 <sup>th</sup> Judicial Circuit In and For Orange County, Florida)	Deposition
February 23, 2018	<i>R Berg v Alta Building Material Co., et al.,</i> Case No: RG17849293 (Alameda County Superior Court, Oakland, CA)	Deposition

March 2018	<i>S Lanzo v Cyprus Amax Minerals Company, et al.</i> , Docket No. MID-L-7385-16AS, (Superior Court of New Jersey Law Division, Middlesex County)	Trial
March 30, 2018	<i>J Anderson v Imerys Talc America, Inc., et al.</i> , Case No. BC666153, (Superior Court of the State of California for the County of Los Angeles)	Deposition
March 30, 2018	<i>C Weirick v Imerys Talc America, Inc., etc.</i> , Case No. BC656425, (Superior Court of the State of California for the County of Los Angeles)	Deposition
April 10, 2018	<i>E Martinez v Honeywell International Inc., etc.</i> , Case No. 17-2-269000-0SEA, (Superior Court Washington for King County)	Deposition
April 10, 2018	<i>D Trepanier v Honeywell International Inc., etc.</i> , Case No. 17-2-25830-0SEA, (Superior Court Washington for King County)	Deposition
April 24, 2018	<i>N Cabibi v Avon Products Inc., et al.</i> , Case No. BC665257, (Superior Court of the State of California for County of Los Angeles)	Deposition
April 27, 2018	<i>I Brick v Brenntag North America, Inc., et al.</i> , Case No. BC674595, (Superior Court of the State of California for the County of Los Angeles)	Deposition
May 18, 2018	<i>I Delacruz v Brenntag North America, Inc., et al.</i> , Case No. BC658576, (Superior Court of the State of California for the County of Los Angeles)	Deposition
May 22, 2018	<i>B Boyd-Bostic v Sonoco Products Company, et al.</i> , C/A No. 17-CP-16-0400, (In the Court of Common Pleas, Fourth Judicial Circuit, State of South Carolina, County of Darlington)	Trial
June 18, 2018	<i>B Arend v Johnson &amp; Johnson, et al.</i> , Docket No. MID-L-1370-17AS, (Superior Court of New Jersey Law Division, Middlesex County)	Deposition
July 9, 2018	<i>K von Salzen and J von Salzen v American International Industries Inc., et al.</i> , Docket No. BC680576, (Superior Court of the State of California for the County of Los Angeles)	Deposition

July 17, 2018	<i>J Alexander, et al.</i> v Honeywell International, Inc., et al., Case No. 868152, (The Court of Common Pleas, Cuyahoga County, Ohio)	Deposition
August 28, 2018	<i>D Waters, et al.</i> v AGCO Corporation, et al., Case No. 2017-CP-CP05462, (The Court of Common Pleas, County of Richland, State of South Carolina)	Deposition
September 10, 2018	<i>A Tucker</i> v Chanel Inc, et al., Case No. 17CV13605, (Circuit Court of the State of Oregon for the County of Multnomah)	Trial
September 11, 2018	<i>C Weirick</i> v Brenntag North America, Inc., et al., Case No. BC656425, (Superior Court of the State of California for the County of Los Angeles)	Trial
September 18, 2018	<i>C Allen</i> v Brenntag North America, Inc., et al., Case No. DR180132, (Superior Court of the State of California for the County of Humboldt)	Deposition
October 1, 2018	<i>C Hayes</i> v Colgate-Palmolive Company, et al., Case No. 16-CI-03503, (Jefferson Circuit Court, Division 10, State of Kentucky)	Deposition
October 22, 2018	<i>M Chapman</i> v BASF CATALYSTS LLC, Case No. MID-L-02911-17-AS; <i>R Rimondi</i> v BASF CATALYSTS LLC, Case No. MID-L-02912-17; <i>J Ruman</i> v BASF CATALYSTS LLC, Case No. MID-L-02919-17 (Superior Court of New Jersey Law Division, Middlesex County)	Deposition
October 23, 2018	<i>C Kerkhof</i> v Brenntag North America et al., Case Bi. 439392-V (Circuit Court for Montgomery County, Maryland)	Deposition
October 26, 2018	<i>A Brower</i> v Johnson and Johnson, Inc. et al., Civil Action File No. 16-EV-005534-E (State Court of Fulton County, State of Georgia)	Deposition
November 15, 2018	<i>T Leavitt</i> v Johnson and Johnson Inc., et al., Case No. RG17882401, (Superior Court of the State of California for the County of Alameda)	Deposition
November 30, 2018	<i>S Pipes</i> v American Honda Motor Co., Inc., et al., Case No. CJ-2017-3487, (District Court of Oklahoma County, State of Oklahoma)	Deposition

December 14, 2018	<i>D Henson</i> v Colgate-Palmolive Company, et al., Case No. BC702253, (Superior Court of the State of California for the County of Los Angeles)	Deposition
December 19, 2018	<i>P Fong</i> v Johnson & Johnson, et al., Case No. JCCP 4674, (Superior Court of the State of California for the County of Los Angeles)	Deposition
January 2, 2019	<i>J Lee</i> v A.W. Chesterton Company, et al., Case No. FSCS050176, (Superior Court of the State of California for the County of Solano)	Deposition
January 7, 2019	<i>R Blinkinsop</i> v Albertsons Companies, Inc., et al., Case No. BC677764, (Superior Court of the State of California for the County of Los Angeles)	Deposition
January 23, 2019	<i>G Koretoff</i> v Arkema, Inc., et al., Case No. BC656506, (Superior Court of the State of California for the County of Los Angeles)	Deposition
February 15, 2019	<i>D Rininger</i> v Hollingsworth & Vose Company, et al., Case No. AC-2014-11-5256, (Court of Common Pleas, Summit County, Ohio)	Deposition

# **EXHIBIT B**



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# EXHIBIT C

CURRICULUM VITAE

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Box 396  
Charlotte, VT 05445

**Education**

MS - University of Vermont, Physiology & Biophysics, 1970  
PhD - University of Vermont, Cell Biology, 1977

**Fields of Specialization**

Environmental toxicology, pathogenesis of mesothelioma, epithelial cell differentiation, chemical and physical carcinogenesis and cell injury, pulmonary fibrosis, oxygen free radicals, molecular biology of antioxidant enzymes in lung, signaling pathways in cell injury and survival

**Career Appointments/Honors**

2017	Elected Fellow to the Vermont Academy of Arts and Sciences, "for her ground-breaking and award-winning research on mesothelioma and other asbestos-induced diseases".
2011	University of Vermont, University Distinguished Professor, in Recognition of Outstanding Contributions to her Discipline (one of less than 10 awards historically at UVM)
2010	University of Vermont College of Medicine, UVM Medical Alumni Association Distinguished Graduate Alumni Award, "for Outstanding Achievements in Research, Education, Public Service and Humanitarianism"
2008	Wagner Award, International Mesothelioma Interest Group Meeting, Amsterdam, NL, for Historic Contributions to Mesothelioma Research
2007	American Thoracic Society Career Achievement Recognition Award for Scientific Accomplishments
2004	Alumni Achievement Award, University of Vermont College of Medicine
1995 - 2013	Director, Environmental Pathology Program, University of Vermont College of Medicine
1995 - 1998	Program Leader, Cell Signaling and Growth Control Research Program, Vermont Cancer Center
1992 -	Professor, Department of Pathology, University of Vermont College of Medicine
1989 -	Adjunct Faculty Member, <i>In Vitro</i> Cell Biology and Biotechnology Program, State University of New York, Plattsburgh, NY
1984 - 1992	Associate Professor, Department of Pathology, University of Vermont College of Medicine
1984 - 1988	Chair, Cell and Molecular Biology Program, University of Vermont College of Medicine
1981 - 1982	First University of Vermont Medical Scholar Award for "outstanding and sustained research and scholarly contributions to both the academic discipline and the life of the University of Vermont"
1980 - 1983	Assistant Professor, Department of Pathology, University of Vermont College of Medicine
1978 - 1980	Research Assistant Professor, Department of Pathology, University of Vermont College of Medicine
1975 - 1977	Research Associate, Department of Pathology, University of Vermont College of Medicine
1973 - 1974	Research Assistant, Department of Pathology, University of Vermont College of Medicine
1970 - 1973	Research Assistant, Institute of Environmental Medicine, New York University, Sterling Forest, NY



1968 - 1970 Research Assistant, Department of Obstetrics and Gynecology, University of Vermont College of Medicine  
1968 - 1970 Graduate Student, Physiology and Biophysics, University of Vermont College of Medicine

### **Editorial Boards**

#### **Current:**

1998 - American Journal of Respiratory Cell and Molecular Biology  
2004 - Particle and Fibre Toxicology  
2005 - Current Respiratory Medicine Reviews  
2006 - International Journal of COPD  
2010 - International Journal of Clinical and Experimental Pathology

#### **Past:**

1993 - 2005 Toxicology and Applied Pharmacology  
1993 - 2010 Free Radical Biology and Medicine  
1996 - 2005 Laboratory Investigation  
1996 - 2006 American Journal of Physiology (Lung Cell Molecular Physiology)  
2004 - 2006 The International Journal of Biochemistry & Cell Biology  
2004 - 2012 American Journal of Pathology

### **Reviewer (Journals)**

*American Journal of Physiology: Lung Cell Molecular Physiology*  
American Journal of Respiratory and Critical Care Medicine  
American Review of Respiratory Diseases  
American Industrial Hygiene Association Journal  
Archives of Biochemistry & Biophysics  
Atherosclerosis  
Cancer Research  
Carcinogenesis  
Cell Biology & Toxicology  
Cell & Tissue Kinetics  
Chemical Research in Toxicology  
Chest  
Clays and Clay Minerals  
Clinical Cancer Research  
Clinical Pathology and Pharmacology  
Critical Review in Toxicology  
Dose Response  
Drug and Chemical Toxicology (past section Head of *In Vitro* Toxicology)  
Environmental Health Perspectives  
Environmental Mutagenesis, Carcinogenesis  
Environmental Research  
European Journal of Cancer & Clinical Oncology  
Experimental Cell Research  
Experimental Lung Research  
*In Vitro* Toxicology  
Inhalation Toxicology  
Journal of the American College of Toxicology  
Journal of Biological Chemistry  
Journal of Cellular Physiology  
Journal of Clinical Investigation  
Journal of Clinical and Laboratory Medicine  
Journal of Leukocyte Biology  
Journal of the National Cancer Institute

Journal of Toxicology and Applied Pharmacology  
Lung Cancer  
Molecular Medicine  
Molecular Cancer Therapeutics  
Nanotoxicology  
Nature  
Nature Nanotechnology  
New England Journal of Medicine  
New Journal of Chemistry  
Nutrition and Cancer  
Oncotarget  
Regulatory Pharmacology and Toxicology  
Risk Analysis  
Scanning Electron Microscopy  
Science

**Appointments on National and International Committees/Panels**

Site visit participant and reviewer of grants for National Science Foundation; Environmental Protection Agency; National Cancer Institute; National Heart, Blood and Lung Institute; Member of Special Review Group on Chemoprevention Projects; National Cancer Institute; Study Section on Small Business Innovative Research (SBIR) Grants, NCI; National Science and Engineering Research Council of Canada; Veterans Administration research awards; Medical Research Council of Canada, American Cancer Society; Western Provinces Lung Association Grant Review Committee; Nickel Producers Environmental Research Association; Center for Indoor Air Research Contributor, Surgeon General's Report, "Smoking Related Cancer and Chronic Lung Disease in the Workplace", Special Emphasis Panels (Clinical Sciences) on a regular basis.

National Academy of Sciences Committee on "Non-Occupational Health Risks of Asbestiform Fibers", **1982 - 1983**

Consultant, EPA Scientific Advisory Board for Review of Airborne Asbestos Health Update, **1985**

External Advisory Committee, Stony Brook-Brookhaven Program Project on "Particle Deposition and Clearance by the Lung", **1985**

External Advisory Committee, University of California at Davis, Program "Pulmonary Effects of Environmental Oxidants", **1987 - 1990**

Scientific Advisory Committee, Alternative Approaches to Animal Testing, Proctor & Gamble, Cincinnati, OH, **1988**

Scientific Advisory Committee, Owens-Corning Fiberglas, Toledo, OH, **1988 - 1989; 1999 - 2000**

External Advisory Committee, Asbestos Research, Health Effects Research Institute, Cambridge, MA, October 31 - November 1, **1988**

Literature Review Panel on Asbestos, Health Effects Research Institute, **1990 - 1992**

Chemical Pathology Study Section, NIH, Ad hoc, **1992, 1995**

Member, Human Exposure and Health Effects Grant Review Panel, US Environmental Protection Agency, **1989 - 1993**

Member, NIOSH Board of Scientific Counselors, Fiber Subcommittee, **1989 - 1993**

Pulmonary Diseases Advisory Committee, NHLBI, **1990 - 1994** (Chair, **1994**)

Scientific Advisory Committee for Research Grants (Personnel for Research), American Cancer Society, **1991 - 1994**

Representative of the American Association of Pathology to the FASEB Life Sciences Research Advisory Committee, **1991 - 1994**

Invited guest of the Lung Division to NHLBI Council Meetings, September, **1993, 1994**

American Thoracic Society, Planning Committee, **1994 - 1997**

American Association for Cancer Research, Program Committee (Lung Cancer), **1994**

Co-Chair (with Dr. Gary Hunninghake), NHLBI, Coordination of Special Emphasis Research Panels for the Lung Division, **1994**

Member, US Environmental Protection Agency, Science Advisory Board, Environmental Health Committee, **1986 - 1996**  
Assembly on Environmental and Occupational Health, Program Committee, American Thoracic Society (ATS), **1992 - 1996**  
Ad Hoc Reviewer of the Laboratory of Human Carcinogenesis, Division of Basic Sciences, National Cancer Institute, September, **1996**  
External Advisory Committee, NIEHS Center at Oregon State University, **1996 - (Chair, 2003 - 2004)**  
Contributor and Panel Member, *Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment*, ILSI Risk Science Institute, Washington, DC, **1998**  
Council Member, The Oxygen Society, 1995-1999; Chair, Annual Mtg., Washington, DC, November, **1998**  
Lung Biology and Pathology Study Section, NIH, July, **1995 - 1999**  
American Society of Investigative Pathology, FASEB Program Committee, **1997 - 2000**  
Board of Scientific Counselors (Subcommittee on Basic Research), National Cancer Institute, **2000 - 2005**  
External Reviewer, Pilot Grant Program, NIEHS Center, Harvard University, **2002**  
Parent Program Project Review Committee Member, National Heart, Lung and Blood Institute, **2002 - 2006, currently Ad Hoc member**  
Scientific Advisory Board, CIIT Center for Health Research, **1995 - (Chair, 2002 - 2003)**  
External Scientific Advisory Committee, EPA Center for Particulate Health Effects, NYU, **2003 - 2005**  
Board of Scientific and Policy Advisors, American Council on Science and Health, **2003 -**  
External Advisory Committee, NIEHS Center for Molecular Toxicology, Vanderbilt University, Nashville, TN, **2003 -**  
External Advisory Committee, Center for Asbestos-Related Diseases (CARD), Libby, Montana, **2003 - (Focus Award, 2006)**  
NIEHS Center Overview Committee, **2004**  
NIEHS Review Committee: Transitional Investigator Position Awards (TIPS), **2004 -**  
NIEHS Superfund grant reviewer, **2005**  
Program Committee, American Society for Investigative Pathologists (ASIP), **2004 - 2006**  
External Advisory Committee, Center of Biologic Research Excellence (COBRE NIH) in "Lung Biology", Dartmouth Medical College, Hanover, NH, **2004 - 2012**  
External Protocol Review Committee, Beryllium BioRepository, Department of Energy, **2006**  
Chair, External Advisory Committee, NIEHS Director's Challenge Project on "Genetics of Susceptibility to Hyperoxia Insult", NIEHS, **2006 - 2010**  
Advisory Committee, Nano-Interact Project of the European Union, **2006 -**  
External Advisory Committee, Department of Environmental and Occupational Health, School of Public Health, University of Pittsburgh, Pittsburgh, PA, **2006 -**  
American Society for Investigative Pathology (ASIP), Education Committee, **2007 - 2009**  
American Thoracic Society, Research Program and Funding Committee, **2007 - 2008**  
Peer Reviewer, NIOSH White Paper: Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research, **2007**  
External Reviewer, EPA National Health and Environmental Effects Research Laboratory (NHEERL), Action plan on Libby amphibole asbestos, **2007**  
Evaluation and Review Panel (REP), National Mesothelioma Virtual Bank, University of Pittsburgh, **2007 -**  
Chair, Special Emphasis Panel, NHLBI: RFA on Targeting Smooth Muscle in Prevention of Asthma, **2009**  
Speaker and Participant, Institute of Medicine/National Research Council, Workshop on the NIOSH Research Roadmap on Asbestos Fibers and Other Elongated Mineral Particles, **2009**  
External Reviewer, National Center for Environmental Assessment's (NCEA) Technical Qualification Board Review, **2011**  
Review Panel, Virtual Consortium for Translational/Transdisciplinary Environment Research Review Meeting, NIEHS, **2011**  
Reviewer, AIRC (Associazione Italiana per la Ricerca sul Cancro) research grants, **2011 - 2012, 2014**  
Review Panel, International Collaborations in Environmental Health, NIEHS, June **2012**  
Reviewer, NIOSH Nanotechnology Research Center (NTRC) FY13 intramural project proposal, November **2012**

Session Co-Chair "Naturally Occurring and Synthetic Fibers including Nanofibers and Nanotubes", Geological Society of America, Northeastern Section Meeting, Bretton Woods, NH, March 17 - 19, **2013**  
Organizing Committee, 10<sup>th</sup> International Meeting on Particle Toxicology, Dusseldorf, Germany, June 4 - 7, **2013**  
Scientific Advisory Board, Mesothelioma Applied Research Foundation (MARF), **2013 - 2018**  
Editor, Science Quarterly of MARF, **2014**  
Chair, Special NIH Review Panel, NHLBI Parent Program Project Study Section, Washington, DC, June 13, **2013**  
Chair, Special NIH Review Panel, RFA on Pulmonary Hypertension Phenomics, Bethesda MD, June 17, **2014**  
External Advisory Committee, NIEHS Superfund grant on "Asbestos: fate, exposure, remediation, and health effects, University of Pennsylvania, **2014 -**  
Ad Hoc Member, Special Emphasis NIH Panel/Scientific Review Group on "Cancer Etiology", Gaithersburg, MD, June 19 - 11, **2015**  
Ad Hoc Member, Board of Scientific Counselors, NCI, Internal Review Program, October 28 - 30, **2015**  
Organizing Committee, 11<sup>th</sup> International Meeting on Particle & Fiber Toxicology, Singapore, September **2016**  
International Mineralogical Association (IMA) Working Group on Asbestos, **2019**

#### **Invited Participant/Speaker in NIH/EPA Workshops**

"Pleural Cell Biology in Health and Disease", NHLBI, October 1 - 2, **1990**  
"Neuroendocrine Cells in Pulmonary Biology", NHLBI, September 5 - 6, **1991**  
"Research Needs and Opportunities Related to Respiratory Health of Women", NHLBI, January 30 - 31, **1992**  
Co-chair, "Environmental Lung Disease: Relationship between Acute Inflammatory Responses to Air Pollutants and Chronic Lung Disease", NHLBI/NIEHS, May 29 - 31, **1991**  
Co-chair, "*In Vivo* Cell Biology", NHLBI, June 7 - 8, **1993**  
"Pulmonary Complications of Breast Cancer Therapy", NHLBI, September 20, **1993**  
"New Approaches to Pulmonary Fibrosis", NHLBI, August 30 - 31, **1994**  
Chair, "Genetics and Gene Therapy for the Study of Pulmonary Diseases", NHLBI, September 23 - 24, **1994**  
Chair, "Strategies for Interventions in Aging and Age-Related Diseases", NIA, July 14 -16, **1999**  
Training Evaluation Working Group, NIEHS, September 14 - 15, **1999**  
Planning Committee and Chair of Working Group, Signal Transduction Workshop, NIEHS, April 11 -12, **2001**  
Working Group on Pulmonary Fibrosis, NHLBI, June 26 - 27, **2001**  
Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length, Agency for Toxic Substances and Disease Registry (ATSDR/EPA), New York, NY, October 7 - 9, **2002**  
Panel Member and Speaker, EPA Workshop on Asbestos Mechanisms of Toxicity, Chicago, IL, June 12 - 13, **2003**  
Working Group member, EPA/ATSDR panel on Libby Asbestos Mine, Libby, MT, August 17 - 19, **2003**  
Panel Member/Session Chair: Validation of Causal Relationships in Criteria to Establish Etiology of Human Cancers, Division of Biological Carcinogenesis and Toxicology, National Cancer Institute, December 11 - 12, **2003**  
Invited Participant, NHLBI/Cystic Fibrosis Foundation workshop on "Adult Stem Cells, Lung Biology, and Lung Disease", University of Vermont College of Medicine, Burlington, VT, July 25 - 27, **2005**  
Invited Working Group Member, NIEHS/NTP Working Group on "Biomarkers for Toxicology Studies", Research Triangle Park, NC, September 20 - 21, **2006**  
Invited Expert, National Toxicology Program's (NTP) Report on Carcinogens (RoC) Registry, **2008**  
Group Leader, Asbestos: A Science-Based Examination of the Mode of Action of Asbestos, NIEHS/EPA, Research Triangle Park, NC, December 16 - 17, **2009**  
Invited Panelist and Lecturer, "Inflammasome Activation from Erionite", Workshop on Erionite, NIEHS, Research Triangle Park, October 12, **2011**  
Chair, Special NHLBI Review Panel, "Systems pharmacogenomics of asthma treatment, November 3, **2017**  
Planning Committee on "Elongate Mineral Particles: Integrating Terminology and Characterization", National Academies of Science, **2017- 2018**

#### **Societies**

Sigma Xi Scientific Honor Society  
American Association for Cancer Research  
American Thoracic Society  
American Society of Investigative Pathology  
Pluto Society for Excellence in Pathology Research (University Associates in Pathology)  
Women in Cancer Research  
Pulmonary Pathology Society  
The International Association for the Study of Lung Cancer (IASLC)

#### **University Committees**

Animal Care Committee, Given Institute  
Admissions Committee for the Medical College  
Steering Committee, Cell Biology Program  
Admissions Committee, Cell Biology Program  
Graduate Education Coordinator for the Department of Pathology  
Search Committee for Chair of Pediatrics  
Evaluation Committee for Chair of Biochemistry  
Senate Committee on Research and Scholarship  
Search Committee for Dean, College of Agriculture and Life Sciences  
Self-Study Committee on Re-accreditation  
Evaluation for Chairman of Pharmacology  
Hearing Officer, Office of Affirmative Action  
Task Force on Research and Scholarship  
Given Asbestos Management Task Force  
University of Vermont Faculty Mentorship Program  
Graduate Alumni Award Committee

#### **Invitations/Presentations**

"Interaction of Crocidolite with the Tracheobronchial Epithelium in Organ Cultures", Proceedings for the Society of Experimental Biology and Medicine, Champlain Division, Stamford, CT, November 15, **1975**  
"Long-term Maintenance of Hamster Tracheal Organ Cultures", GAP Workshop on Tissue Culture Models to Study Cystic Fibrosis Lake Placid, NY, October 12 - 14, **1977**  
"Interaction of Environmental Particulates with the Tracheobronchial Epithelium", School of Public Health, Harvard University, Boston, MA, January 30, **1978**  
"Models of Respiratory Carcinogenesis" Dartmouth Medical School, Hanover, NH, October 15, **1978**  
"Organ Culture as a Tool to Study Environmental Carcinogenesis" Workshop on Teaching of Environmental Pathology, Aspen, CO July 29 - August 3, **1979**  
Invited Participant, International Workshop on "Effects of Mineral Dusts *In Vitro*", MRC Pneumoconiosis Unit, Cardiff, Wales, September, **1979**  
"Comparative Cytotoxicity of Chrysotile and Crocidolite Asbestos in Hamster Tracheal Epithelial Cells", Gordon Conference: Pulmonary Biology: Lung Injury, Colby Sawyer College, New London, NH, August 11 - 15, **1980**  
"Interaction of Minerals with Cell Membranes", Clay Minerals Society, Waco, TX, October 5 - 9, **1980**  
"Asbestos and Carcinogenesis - Mechanisms of Cellular Injury", Department of Pulmonary Medicine, Yale University, New Haven, CT, January 21, **1981**  
"Mechanisms of Asbestos Carcinogenesis", American Health Foundation, Naylor-Dana Institute, Valhalla, NY, January 23, **1981**  
Invited Participant, Conference on Epidemiological, Immunological Genetical Aspects of Asbestosis Wroclaw, Poland, March, **1981**  
"Studies of Cellular Mechanisms in Asbestos-induced Disease", State University of New York, Department of Health, Division of Laboratories and Research, Albany, NY, June 20, **1981**  
Key Note Speaker, "Asbestos-induced Cancers", Annual Meeting of the American Cancer Society, Vermont Division, Montpelier, VT, October 15, **1981**



"Mechanisms of Asbestos-induced Carcinogenesis in Hamster Trachea", 12<sup>th</sup> Conference on Environmental Toxicology, Dayton, OH, November 3, **1981**

Invited Participant, 2<sup>nd</sup> International Workshop on "Effects of Mineral Dusts *In Vitro*", NCTR Little Rock, AK, April, **1982**

"Mechanisms of Asbestos and Nonasbestiform Particles and Fibers in Bronchogenic Carcinoma", 4<sup>th</sup> Annual RMCOEH Occupational and Environmental Health Conference on Health Issues Related to Metal and Nonmetallic Mining, Park City, UT, April 7 - 9, **1982**

"Asbestos - Mechanisms of Cytotoxicity and Carcinogenicity in the Respiratory Tract", School of Public Health, University of California at Berkeley, Berkley, CA, June 11, **1982**

"*In Vitro* Studies Pertaining to Ingested Asbestos", Summary Workshop on Ingested Asbestos, US EPA, Cincinnati, OH, October 13 - 14, **1982**

Session Chairperson and Speaker, "Chemical-induced Injury", International Conference on Beta Cell Injury, Juvenile Diabetes Foundation, Princeton, NJ, October 27 - 30, **1982**

"Alternate Approaches to Animal Testing: Tracheal Organ Culture", Battelle Laboratories, Columbus, OH, March 29, **1983**

"Mechanisms of Asbestos Carcinogenesis", University of South Alabama College of Medicine, Graduate Program in Basic Medical Sciences, Mobile, AL, November 10, **1983**

"Cocarcinogenesis and Tumor Promotion by Particulates and Fibers in the Respiratory Tract", Conference on Tumor Promotion and Enhancement in Human and Experimental Respiratory Tract Carcinogenesis, US EPA, Williamsburg, VA, June 17 - 20, **1984**

"*In Vitro* Studies on Asbestos-induced Carcinogenesis", W. Alton Jones Cell Science Center, Lake Placid, NY, July 17, **1984**

"Mechanisms of Cell Damage and Carcinogenesis by Asbestos", National Institute of Occupational Safety and Health, Morgantown, WV, September 10, **1984**

Member, Organizing Committee, 3<sup>rd</sup> International Workshop on Effects of Mineral Dusts *In Vitro*, Hochschwarzwald, Germany, September, **1984**

"Cellular Mechanisms of Damage and Carcinogenesis by Asbestos and Polycyclic Aromatic Hydrocarbons", National Institute of Environmental Health Sciences, Research Triangle, NC, January 17, **1985**

"Mechanisms of asbestos-induced toxicity and carcinogenicity" Department of Pathology, State University of New York at Syracuse, Syracuse, NY, March 18, **1985**

"Pathogenesis of asbestos-associated disease "Division of Pulmonary Medicine, Yale University, New Haven, CT, March 27, **1985**

Invited Participant, International Conference on Biological Mechanisms of Occupational Lung Disease Park City, UT, April, **1985**

"Oxygen free radicals in asbestos-induced lung injury" AIR Seminar Series, University of Rochester Medical Center, Rochester, NY, April 30, **1985**

"Role of Active Oxygen Species in Asbestos-associated Toxicity", Fine Particles Symposium, Miami, FL, April 22, **1985**

"*In Vitro* Approaches to Study of Respiratory Tract Cancers", National Institutes of Health, Interagency Collaborative Group on Environmental Carcinogenesis, Bethesda, MD, October 16, **1985**

"Mechanisms of asbestos-associated carcinogenesis", New York University Medical Center, Division of Environmental Medicine, Sterling Forest, NY, October 23, **1985**

"Importance of Fiber Length and Dimension in Asbestos-induced Toxicity and Carcinogenesis", US Army, Department of Toxicology, Aberdeen, MD, December 18, **1985**

Scientific Program Chairman, 37<sup>th</sup> Annual Meeting of the Tissue Culture Association, Chicago, IL, **1986**

"Mechanisms of Asbestos Carcinogenesis", Session-In-Depth on Mechanisms of Cell-Toxicant Interaction, 37<sup>th</sup> Annual Meeting of the Tissue Culture Association, Chicago, IL June 7, **1986**

"Oxygen Free Radicals as Causative Factors in Asbestosis", University of Connecticut, Department of Laboratory Medicine, Farmington, CT, June 23, **1986**

"Approaches to Prevention of Asbestos-induced Fibrotic Lung Disease in Rats Using Administration of Polyethylene (PEG)-conjugated Scavengers of Active Oxygen Species", ENZON Conference on "Modified Enzymes in Free Radical Research", Princeton, NJ, July 19, **1986**



Invited Participant, 14<sup>th</sup> International Cancer Congress, Panel on Experimental and Human Respiratory Tract Carcinogenesis, Budapest, Hungary, August, **1986**

Invited Session Chair, 4<sup>th</sup> International Conference on Pulmonary Fibrosis, Gothenburg, Sweden, October, **1986**

"Mechanisms of asbestos-induced carcinogenesis," Defense Research Institute, Seminar on "Asbestos Medicine," Boston, MA, November 21, **1986**

"Role of oxygen free radicals in asbestos-induced lung disease," Conference on "Oxygen Radicals and Antioxidants in Cancer and Aging," University of California at Berkeley, Berkeley, CA, February 6 - 7, **1987**

"Mechanisms of Pulmonary Carcinogenesis by Inorganic Particles," Workshop on "Mechanisms and Distributions of Environmental Disease," Montreal, Quebec, Canada, April 28, **1987**

"Asbestos Fibers and Disease," Policy Forum: Asbestos in Commercial Buildings, Urban Land Institute, Washington, DC, June 16, **1987**

Invited Lecturer, British Association of Lung Research Meeting on "Mineral Fibers," Surrey, England, July 13 - 14, **1987**

Invited Session Chair, IARC-WHO Symposium, "Mineral Fibers in the Non-Occupation Environment Lyon, France, September 8 - 10, **1987**

"Mechanisms of Asbestos Fibers in Disease," Symposium on Scientific Advances in Environmental Medicine, New York University Institute of Environmental Medicine, New York, NY, October 29 - 30, **1987**

Scientific Program Chair, NATO-NIH Advanced Research Workshop on Effects of Mineral Dusts *In Vitro*, Sherbrooke, Quebec, Canada, **1988**

Invited Discussant, "Oxygen Radicals in Xenobiotic-induced Tissue Injury", Upjohn - UCLA Symposium on Oxy-Radicals in Molecular Biology and Pathology, Park City, UT, January 24 - 30, **1988**

"Free Radical Mechanisms in Asbestos-induced Diseases, Symposium on Free Radical Mechanisms in Pathogenesis, Annual meeting of the Society of Toxicology, Dallas, TX, February 16 - 19, **1988**

Invited Speaker, BOMA International Asbestos Management Seminar, New York, NY, March 10 - 11, **1988**

Invited Participant, International Symposium on "Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke," Battelle-Seattle, WA, April 10 - 14, **1988**

"Mechanisms of Cell Damage and Proliferation by Asbestos", W. Alton Jones Cell Science Center, Lake Placid, NY, May 10, **1988**

Invited Participant, Proctor and Gamble Workshop on "Future Directions in Research on Toxicology of the Respiratory Tract", Cincinnati, OH, October 17 - 19, **1988**

"Fibers", meeting on "Biology, Toxicology and Carcinogenesis of the Respiratory Epithelium", Albuquerque, NM, November 14 - 16, **1988**

"Factors Influencing Individual Responses to Asbestos", Symposium on "Health Aspects of Asbestos in Buildings", Energy and Environmental Policy Center, John F. Kennedy School of Government, Harvard University, Cambridge, MA, December 14 - 16, **1988**

"Mechanisms of Asbestos-induced Diseases", Wadsworth Center for Laboratories and Research Scientific Seminar Series, State of New York Department of Health, Albany, NY, January 24, **1989**

Invited Session Chair, 1<sup>st</sup> International Conference on Health Related Effects of Phyllosilicates, Paris, France, March 16 - 17, **1989**

Invited Session Chair and Speaker, Colloquium Ramazzini International Meeting on "Different Pathogenic Potential of Asbestos Fibers" Ottawa, Ontario, Canada, March 20 - 22, **1989**

"The Medical Case from the Doctor's Standpoint" Asbestos in Buildings: The Laws, the Costs, the Solutions, Law Journal Seminars-Press, New York, NY, April 13 - 14, **1989**

"Asbestos toxicology", Toxicology Update, Current Concepts in Inhalation Toxicology, Johns Hopkins University, Baltimore, MD, April 24 - 26, **1989**

Session Leader/Invited Speaker, NIEHS Workshop on Research Needs in Fiber Toxicology, Research Triangle Park, NC, July 10 - 12, **1989**

"Antioxidant Enzyme Defense Mechanisms in Asbestos-related Lung Injury", Chicago Lung Association Conference on Occupational Lung Disease, Chicago IL, October 19 - 22, **1989**

"Asbestos: Scientific Developments and Public Policy", American Industrial Hygiene Association, Meriden, CT, March 14, **1990**

"Mechanisms of Asbestos-induced Lung Disease", Department of Pathology, Mount Sinai School of Medicine, New York, NY, March 19, **1990**

"Role of Oxy-radicals in Rodent Cells", Cold Spring Harbor Conference on Mechanisms of Fiber Cytotoxicity and Carcinogenesis, Banbury Conference Center, Long Island, NY, March 20 - 22, **1990**

"Active Oxygen Species in Asbestos-induced Cell Damage and Disease", Symposium on "Free Radical Mechanisms of Tissue Injury", Annual meeting of the American Chemical Society, Boston, MA, April 22, **1990**

"Mechanisms of Asbestos-related Diseases", Society for Risk Analysis', Forum on Risk of Indoor (Asbestos) Building Materials, Washington, DC, May 7 - 8, **1990**

"Mechanisms of Asbestos-induced Lung Disease", Symposium on "Particle-Lung Interactions: Overload Related Phenomena", Rochester, NY, May 17- 18, **1990**

"Asbestos: Scientific Developments", Clinical Research Institute of Montreal, Montreal, QC, Canada, May 22, **1990**

"Asbestos: An Overview on Mechanisms of Action in the Causation of Lung Diseases", Symposium on "Exogenous and Endogenous Factors as Major Cancer Risks in Carcinogenesis", 81<sup>st</sup> Annual Meeting of the American Association of Cancer Research, Washington, DC, May 26, **1990**

Invited Speaker, International Meeting on "Free Radicals in Health and Disease" Johannesburg, South Africa, July 18 - 20, **1990**

"Health Effects of Low Level Exposure", Workshop on Asbestos in Buildings, Canadian Centre for Occupational Health and Safety, Laval, Quebec, Canada, September 11, **1990**

"Recent Information on Potential Health Risks from Exposure to Asbestos", American Association of School Administrators "I Care" Conference, Hyatt Regency on Capitol Hill, Washington, DC, September 13, **1990**

"Risks from Asbestos Exposure" Society for Risk Analysis Annual Meeting, New Orleans, LA, October 7, **1990**

Organizing Committee, 6<sup>th</sup> International Colloquium on Pulmonary Fibrosis, Stowe, VT, October 14 -17, **1990**

Scientific Chair, Session on "Evidence for Mechanisms from Cell Culture Studies" NATO Meeting on "Mechanisms of Fibre Carcinogenesis", Albuquerque, NM, October 22 - 25, **1990**

"The Risks of Asbestos in Buildings: The Need for National Policy", Brookings Institute, Washington, DC, November 7, **1990**

Visiting Pulmonary Scholar sponsored by Burroughs Wellcome; the Chemical Industry Institute of Toxicology; Duke University; the US Environmental Protection Agency; the National Institute of Environmental Health Sciences; North Carolina State University Veterinary School and the University of North Carolina, Raleigh, NC, February 5 - 7, **1991**

"Asbestos and Lung Disease", Grand Rounds, St. Luke's/Roosevelt Hospital, Department of Medicine, New York, NY, February 13, **1991**

"Oxidant-induced Cell Injury by Asbestos", Department of Pathology, Baylor College of Medicine, Houston, TX, March 21, **1991**

"Molecular Biology of Asbestos Interactions with Tracheal Epithelial Cells and Lung Fibroblasts", Wayne State University, Detroit, MI, April 8, **1991**

"Oxidants, Antioxidants, and Asbestos-induced Lung Disease", Institut Lady Davis de Recherches Medicales, Montreal, Quebec, Canada, April 16, **1991**

"Oxidants, Antioxidants and Asbestos-related Lung Disease", American Health Foundation, Valhalla, NY, May 9, **1991**

Chair and Session Summarizer, "Mechanisms of Asbestos-induced Lung Disease", American Thoracic Society, American Lung Association Annual Meeting, Los Angeles, CA, May 14, **1991**

Invited Speaker, 10<sup>th</sup> International Symposium for Society of Toxicologic Pathologists, Pulmonary Toxicologic Pathology, "Mechanisms of Asbestos-induced Lung Injury in a Rat Inhalation Model of Disease", Monterey, CA, June 4, **1991**

"Oxidant Injury and Asbestos-induced Lung Disease", National Institute of Environmental Health Sciences, Research Triangle Park, NC, September 3, **1991**

Session Chair and Invited Lecturer, "Oxidants and Enzyme Induction", 4<sup>th</sup> International Conference on Environmental Lung Disease: At Home, At Work: Mechanisms, Manifestations and Management, Montreal, Quebec, Canada, September 25 - 28, **1991**

Scientific Program Committee, American College of Chest Physicians (ACCP) 4<sup>th</sup> International Conference on Environmental Lung Disease, Montreal, Quebec, Canada, September 24 - 26, **1991**

Session Scientific Chair, "Epidemiology of Malignant Mesothelioma", International Conference on "Mesothelial Cell and Mesothelioma: Past, Present and Future", Paris, France, September 30 - October 2, **1991**

"Mechanisms of Asbestos-induced Lung Cancer and Mesothelioma", American Society of Clinical Oncology, Educational Workshop, Miami, FL, November 8, **1991**

Invited Participant and Rapporteur, Workshop on "Approaches to Evaluating the Toxicity and Carcinogenicity of Man-made Fibers", sponsored by Duke University Center for Extrapolation Modeling, Thermal Insulation Manufacturers Association and US Environmental Protection Agency, Durham, NC, November 11 - 13, **1991**

"Approaches to Testing Synthetic Fibers for Disease Potential", Toxicology Division, Dow Chemical Company, Midland, MI, January 20, **1992**

"Biochemical Mechanisms in Asbestos-related Carcinogenesis and Fibrosis", Department of Biochemistry, Loyola University of Chicago, IL, February 10, **1992**

"Asbestos", Invited Speaker at Symposium on "How Well does Environmental Policy Track Science", Annual meeting of the American Association for Advancement of Science, Chicago, IL, February 11, **1992**

Invited Speaker, "Health Effects of Fibrous Materials", Workshop on Interaction of Glass Surfaces with Chemical and Biological Environments, NSF/University Center for Glass Research, Bethesda, MD, March 5 - 6, **1992**

Plenary Lecturer, 2<sup>nd</sup> International Meeting on "Free Radicals in Inflammation", Society for Rheumatology, Inflammation, and Free Radical Research, Cape Town, South Africa, March 22 - 26, **1992**

Co-chair and Presenter, Mini-symposium: "Adaptive Responses to Injury", American Association of Pathology, FASEB Meeting, April 9, **1992**

Invited Speaker, "Mechanisms of Asbestos-induced Lung Disease and Preventive Approaches", National Center of Occupational Health, Johannesburg, South Africa, March 28, **1992**

Invited Speaker, "Mechanisms of Asbestos-induced Free Radical Production", Mobil Environmental Technical Center, Princeton, NJ, April 27, **1992**

Invited Speaker, "Effects of Asbestos and Free Radicals on Cellular Proliferation", National Cancer Institute Division of Experimental Pathology, National Institutes of Health, Bethesda, MD, May 7, **1992**

Invited Speaker, "Cancer Risks of Asbestos", Symposium on Risk Assessment of Carcinogens in the Workplace and Environment, Annual meeting of the American College of Occupational Medicine, Washington, DC, May 8, **1992**

"Sensitivity of Human Mesothelial Cells to asbestos and Oxidants", Symposium on "Pleural Disease", American Thoracic Society-American Lung Association International Conference, Miami, FL, May 18, **1992**

"Mechanisms of Asbestos Toxicity and Health Risks", American Society of Testing Materials (ASTM) EPA workshop, Johnson VT, July 12 - 14, **1992**

Scientific Chair, Session on "*In Vitro* Assessment of Biopersistence", WHO-IARC Meeting, on "Biopersistence of Respirable Synthetic Fibres and Minerals", Lyon France, September 7 - 9, **1992**

Invited Plenary Speaker, "Asbestos-recent Scientific Developments", Joint Scientific Session of the Pennsylvania and New Jersey Thoracic Societies and the Eastern Division of the ATS, 100<sup>th</sup> Anniversary, Philadelphia, PA, September 11 - 12, **1992**

Invited Faculty, Law Institutes Program on Asbestos Medicine "What Do Animal Inhalation Experiments Tell Us About Human Disease?" Defense Research Institute, Chicago, IL, October **1992**

"Molecular Regulation of Cell Proliferation by Asbestos", Department of Biochemistry and Cell Biology, Albany Medical College, Albany, NY, February 1, **1993**

Invited Speaker, 4<sup>th</sup> International Life Sciences Institute (ILSI) Symposium "Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract", Hannover, Germany, February 28, **1993**

Invited Session Speaker, "Pathology of Lung Injury", American Society for Investigative Pathology, FASEB meetings, New Orleans, LA, March 31, **1993**

Invited Colloquium Participant, International Centre for Scientific Ecology, Paris, France, May 10, **1993**

Member, Advisory Committee, International Meeting on "Oxygen Radical and Lung Injury" NIOSH-NIH, Morgantown, WV, August 29 - September 2, **1993**

Distinguished Professor Lectureship, Jefferson Medical College, Division of Environmental Medicine and Toxicology, Philadelphia, PA, April 28 - 29, **1993**

"Molecular Mechanisms of Asbestos-induced Lung Disease", Seminar series on Pulmonary Biology and Medicine, MD Hershey Medical Center, Penn State University, Hershey, PA, May 7, **1993**

"Protooncogene Induction by Asbestos", 2<sup>nd</sup> International Mesothelioma Workshop, San Francisco, CA, May 15, **1993**

Session Co-chair and Invited Speaker, "Tissue Structural Cells as Effectors of Response to Inhaled Environmental and Occupational Pollutants", American Thoracic Society/American Lung Association International Conference, San Francisco, CA, May 16 - 19, **1993**

Invited Speaker, "Molecular Mechanisms of Cell Proliferation and Carcinogenesis by Asbestos", Center for Radiological Research, College of Physicians and Surgeons of Columbia University, New York, NY, July 14, **1993**

Invited Plenary Speaker, "The Toxicology of Serpentine and Amphibole Asbestos", American Institute of Chemists/American Chemical Society Annual Meeting, 70<sup>th</sup> National Meeting, Chicago, IL, August 24, **1993**

Invited Speaker and Session Chair, Symposium on "Cell Signaling and the Molecular Stress Responses", Lake Placid, NY, September 23 - 26, **1993**

"Mechanisms of Asbestos-induced Lung Disease", Division of Pulmonary Medicine, Department of Internal Medicine, Yale University, New Haven, CT, September 30, **1993**

Invited Speaker, International Symposium on "Coal Dust-induced Respiratory Disorders", Maastricht, The Netherlands, October 8, **1993**

Scientific Organizing Committee, 5<sup>th</sup> International Workshop on Effects of Mineral Dusts *In Vitro*, Creteil, France, October 11 - 13, **1993**

Co-convenor, Symposium, "Health Effects of Mineral Dusts", Mineralogical Society of America, Nantucket, MA, October 22 - 24, **1993**

Invited Speaker, Workshop on "Health Risks Associated with Chrysotile Asbestos", International Commission on Environmental Health, Jersey, Channel Islands, Great Britain, November 14 - 17, **1993**

"Molecular Mechanisms of Asbestos-induced Diseases", Pharmacology and Toxicology Seminar Series, Dartmouth-Hitchcock Medical Center, Hanover, NH, January 19, **1994**

Invited Faculty, Workshop on "Talc: Consumer Uses and Health Perspectives", International Society of Regulatory Toxicology and Pharmacology, FDA, National Institutes of Health, Bethesda, MD January 31 - February 1, **1994**

Invited Speaker, Gordon Conference on "Oxygen Radicals and Biology", Ventura, CA, February 6 - 11, **1994**

Invited Speaker and Session Chair, International Conference on "Crystalline Silica", Baltimore, MD, April 18 - 20, **1994**

Invited Speaker, Wyeth Ayerst Drug Safety Symposium on "Modern Trends in Safety Assessment of Drugs", Chazy, NY May 9, **1994**

"Molecular Mechanisms of Asbestos-induced Lung Diseases", Toxicology Scholars Colloquium, University of Connecticut at Storrs, Center for Biochemical Toxicology, Storrs, CT, May 12 - 13, **1994**

Session Chair, "Pneumoconiosis: Basic Mechanisms", American Thoracic Society/American Lung Association 1994 International Meeting, Boston, MA, May 23, **1994**

Session Co-Chair and Presenter, Symposium on "Transmembrane Signaling and Intracellular Regulation Mechanisms", American Thoracic Society/American Lung Association, 1994 International Meeting, Boston, MA, May 24, **1994**

Invited Speaker, Symposium on "Mesothelioma and Mesothelioma Cells", American Thoracic Society/American Lung Association 1994 International Meeting, Boston, MA, May 24, **1994**

Elected Member, Pluto Club (Honorary Society for Investigative Pathologists), **1994**

"Molecular Mechanisms of Asbestos-Induced Disease", Sealy Center for Molecular Biology, University of Texas at Galveston, Galveston, TX, October 4, **1994**

"Molecular Mechanisms of Asbestos Interactions with Cells", Pulmonary Division, University of Texas at Houston, Houston, TX, October 5, **1994**

Invited Speaker, "Inhalation Models to Explore Mechanisms, Prevention and Treatment of Pulmonary Fibrosis", Wyeth Ayerst Scientific Symposium on Pharmaceutical Aspects of Drug Delivery to the Lung, State University of New York at Plattsburgh, Plattsburgh, NY, October 11, **1994**

Invited Speaker, Postgraduate course on "Cellular Oxidants: Production and Consequences", Queenstown, New Zealand, November 1 - 3, **1994**

Invited Symposium Speaker and Session Chair, VII<sup>th</sup> International Meeting of the Society for Free Radical Research, Sydney, Australia, November 7 - 11, **1994**



Invited Speaker, 5<sup>th</sup> International Life Sciences Institute (ILSI) Symposium, "Correlations Between *In Vitro* and *In Vivo* Investigations in Inhalation Toxicology", Hannover, Germany, February 20 - 24, **1995**

Invited Plenary Lecturer, 5<sup>th</sup> International Conference on "Environmental and Occupational Disease", American College of Chest Physicians, Orlando, FL, March 2 - 5, **1995**

Invited Plenary Lecturer, "Role of Reactive Oxygen and Nitrogen Species in Cell Signaling and Proliferation by Asbestos, 43<sup>rd</sup> Annual Meeting of the Radiation Research Society, San Jose, CA, April 1 - 6, **1995**

Invited Session Chair and Guest, "Meet the Researchers", Pulmonary Pathobiology Subsection, Experimental Biology '95, Atlanta, GA, April 9 - 13, **1995**

Invited Lecturer, "An Update on Asbestos", Robert Wood Medical Institute, Rutgers University, Piscataway, NJ, May 11, **1995**

Invited Speaker and Session Chair, American Thoracic Society Annual Meeting, Miami, FL, May 20 - 24, **1995**

Invited Speaker, 3<sup>rd</sup> International Mesothelioma Conference, Creteil, France, September 12 - 15, **1995**

Invited Speaker, British Association for Lung Research, "Fibres, Particles and the Lung: New Perspectives", Edinburgh, Scotland, September 11 - 12, **1995**

Invited Speaker, Symposium on "Health Effects of Fibrous Minerals Used in Industry Excluding Asbestos", Sydney Australia October 30 - 31, **1995**

Invited Speaker, Keystone Symposium on "Oxidant Stress: from Molecules to Man", Santa Fe, NM, January 8 - 14, **1996**

Invited Participant, Workshop on "Mechanisms of Fibre Carcinogenesis", IARC, Lyon, France, January 9 - 11, **1996**

Invited Session Chair, Gordon Conference on "Oxygen Radicals and Biology", Ventura, CA, February 14 - 19, **1996**

Invited Lecturer, Center for Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ, April 4, **1996**

Session Chair and Invited Speaker, Annual Meeting of the American Thoracic Society, New Orleans, LA, May 10 - 15, **1996**

Invited Plenary Lecturer, Organizing Committee and Editorial Board, 6<sup>th</sup> International Meeting on "Toxicology of Natural and Man-made Fibrous and Non-fibrous Particles", Lake Placid, NY, September 6 - 19, **1996**

Invited Lecturer, Short Course on "Minerals and Health", Institute of Mineralogy and Petrography, University of Fribourg, Switzerland, October 7 - 11, **1996**

Invited Speaker, Oxygen Society Meeting '96, Miami Beach, FL, November 21 - 25, **1996**

Invited Symposium Speaker, Society of Toxicology Annual Meeting, Cincinnati, OH, March 9 - 12, **1997**

Organizer and Chair, Symposium on "Oxidative Mechanisms of Cell Signaling and Repair in Disease", American Society for Investigative Pathology, Experimental Biology '97, New Orleans, LA, April 6 - 9, **1997**

Organizer and Chair, Trends in Experimental Pathology Symposium, "New Developments in Cell Imaging Techniques for Detection of Cell Injury and Disease", American Society for Investigative Pathology, Experimental Biology '97, New Orleans, LA, April 6 - 9, **1997**

Organizer, Workshop on "Environmental Pathology: New Directions and Opportunities, American Society for Investigative Pathology, Experimental Biology '97, New Orleans, LA, April 6 - 9, **1997**

Invited Lecturer and Honorary Membership Award, The Oxygen Society of Greater Washington, DC, Inc., Annual Meeting, Washington, DC, June 10, **1997**

Invited Session Chair, Cell Viability and Death, XIX<sup>th</sup> Annual Meeting, International Society for Heart Research, Vancouver, BC, Canada, July 23 - 27, **1997**

Scientific Organizing Committee and Session Chair, 2<sup>nd</sup> International Conference on Oxygen/Nitrogen Radicals and Cellular Injury, Durham, NC, September 7 - 10, **1997**

Invited Contributor and Session Chair, International Workshop on "Health Effects of Chrysotile Asbestos: Contribution of Science to Risk Management Decisions", Montreal, QC, Canada, September 14 - 16, **1997**

Invited Lecturer, Yale University Symposium on Pulmonary Biology and Environmental Lung Disease, New Haven, CT, October 22, **1997**

Invited Symposium Speaker, Annual Meeting of the Society for Gerontology Research, Cincinnati, OH, November 12 - 17, **1997**

Outstanding Volunteer Contribution Award, The Oxygen Society, Washington, DC, **1998**

Invited Speaker, University of California at Davis, Center for Comparative Respiratory Biology and Medicine, Pulmonary Seminar Series, "Cell Signaling Cascades in Oxidant-induced Lung Injury and Apoptosis" Davis, CA, May 1, **1998**

Invited Speaker, Columbia University; Division of Environmental Health Sciences: "Cell Signaling Events Regulating Apoptosis and Proliferation by Oxidant Stresses in Mesothelial and Pulmonary Epithelial Cells", May 13, **1998**

Invited Speaker, Wayne State University, NIEHS Center Seminar Series: "Cell Signaling by Oxidant Stresses in Lung", Detroit, MI, May 14, **1998**

Invited Speaker, University of Rochester Division of Environmental Health Sciences: "Cell Signaling by Minerals and Oxidants in Environmental Lung Disease", Rochester, NY, May 21, **1998**

Invited Speaker, University of Pennsylvania, "Cell Signaling Mechanisms in Environmental Lung Disease", Philadelphia, PA, September 25, **1998**

Invited Speaker, Pleura 1998: Medical Thoracoscopy - Mesothelioma", "Mechanisms of Asbestos Pathogenesis", Brescia, Italy, October 15 - 16, **1998**

Program Chair, Oxygen '98, Annual Meeting of the Oxygen Society, Washington, DC, November 19 - 23, **1998**

Faculty Member and Speaker, "Mechanisms of Asbestos Carcinogenesis", International Conference on Malignant Pleural Mesothelioma", Lignano, Italy, March 18 - 19, **1999**

Invited Speaker, NIEHS/NHLBI "Apoptosis and Growth Factors/Signal Transduction Pathways: Basic Biology and Toxicology", Raleigh, NC, April 19 - 21, **1999**

Invited Speaker, Department of Environmental Health, Harvard School of Public Health, "Cell Signaling by Environmental Particulates", Boston, MA, May 18, **1999**

Co-leader (with Mark Van Baalen and Carl Francis, Harvard University), "Mineralogy, Petrology and Health Issues at the Ultrameric Complex, Belvidere Mountain, VT", New England Intercollegiate Geological Conference, Burlington, VT, October 1 - 4, **1999**

Keynote Speaker, "Fibre-induced Carcinogenesis", 5<sup>th</sup> International Mesothelioma Interest Group (IMIG) Meeting, Manchester, England, October 5 - 8, **1999**

Invited Speaker, Symposium on "Asbestos at the End of the Century: Basic Science for Substitutes, Removal and Therapies", Torino, Italy, October 11, **1999**

Scientific Organizing Committee and Invited Speaker, "Cell Signaling by Fibres", 7<sup>th</sup> International Meeting on Particle Toxicology, Maastricht, The Netherlands, October 14 - 17, **1999**

Invited Speaker, Department of Cell and Molecular Biology, Loyola University Chicago, "Cell Signaling in Asbestos and Silica-Induced Lung and Pleural Disease", Chicago, IL, April 7, **2000**

Scientific Organizing Committee, International Conference on Basic and Clinical Aspects of Cell Cycle Control, Siena, Italy, May 29 - 30, **2000**

Session Chair and Speaker, "Fibrosis - Inflammation, Oxidants and Cytokines", Gordon Conference on Mechanisms of Toxicity, Plymouth State College, Plymouth, NH, July 23 - 28, **2000**

Invited Speaker and Session Chair, British Association for Lung Research, Edinburgh, Scotland, September 6 - 8, **2000**

Scientific Organizing Committee, International Conference on Environmental and Occupational Respiratory Disease, Lucknow, India, October 29 - November 2, **2000**

Session Co-chair, "Lung Epithelial Signaling by Particles and Fibers", Experimental Biology Meetings, Orlando, FL, April 12, **2001**

Faculty and Panel Member, "Malignant Mesothelioma - Therapeutic Options and Role of SV40: An Update", Chicago, IL, April 20 - 21, **2001**

Plenary Speaker, "Reactive Oxygen Species in Lung Injury and Carcinogenesis", 8<sup>th</sup> Annual Meeting of the Oxygen Society, Raleigh, NC, November 15 - 19, **2001**

Invited Speaker, "Cell Signaling by Oxidative Stress and Inhaled Particles", Johns Hopkins School of Public Health, Baltimore, MD, March 15, **2002**

Scientific Organizing Committee and Invited Speaker, 3<sup>rd</sup> International Symposium on Reactive Oxygen/Nitrogen Species in Cell Injury and Disease, NIOSH, Morgantown, WV, June 1 - 6, **2002**

Invited Participant and Speaker, 12<sup>th</sup> International Colloquium on Pulmonary Fibrosis, Geneva, Switzerland, October 7 - 9, **2002**



Invited Speaker, 1<sup>st</sup> Annual Pittsburgh International Lung Conference: Pulmonary Fibrosis: Bench to Bedside, Pittsburgh, PA, October 12 - 15, **2002**

Invited Speaker and Session Chair, 6<sup>th</sup> International Mesothelioma Group Meeting, Perth, Australia, December 1 - 4, **2002**

Invited Speaker, International Belle Conference on "Non-linear Dose Response Relationships in Biology, Toxicology, and Medicine, University of Massachusetts at Amherst, MA, May 28 - 30, **2003**

Invited Speaker, 1<sup>st</sup> International Conference on Molecular Research in Environmental Medicine: "Cell Signaling Pathways in Responses to Particles and Fibers", Dusseldorf, Germany, March 18 - 21, **2004**

Invited Speaker, 7<sup>th</sup> Meeting of the International Mesothelioma Interest Group (IMIG): "Asbestos-induced Carcinogenic Alterations", Brescia, Italy, June 24 - 26, **2004**

Invited Speaker, British Association for Lung Research, BALR Annual Summer Conference: "Cell Signaling Pathways in Pulmonary Toxicity", University of Leicester, England, September 13 - 15, **2004**

Invited Speaker and Faculty Member, 1<sup>st</sup> International Symposium on Malignant Mesothelioma: "Pathogenesis and Molecular Biology of Mesothelioma", Nevada Cancer Research Center, Las Vegas, NV, October 14 - 16, **2004**

Faculty, Society of Free Radical Biology and Medicine Annual Meeting, Workshop on "Negotiating for Success", St. Thomas, VI, November, **2004**

Session Chair, Society of Free Radical Biology and Medicine, 11<sup>th</sup> Annual Meeting, "Free Radical Toxicity and Clinical Implications", November, **2004**

Invited Speaker, Experimental Biology 2005, Session on "Environmental Toxicology, Modulation of Cell Signaling Pathways for Control of Cell Proliferation and Transformation by Asbestos", San Diego, CA, April 4, **2005**

Invited Speaker, Workshop on Directions and Needs in Asbestos Research: New Insights, "Intervention of Asbestos-associated Cell Signaling: Pathways in Mesothelioma", University of Montana at Missoula, Missoula, MT, July 28 - 29, **2005**

Invited Speaker, Annual Meeting of the Oxygen Club of California and the University of Torino: "Oxidant-induced Signaling Pathways and Chemoresistance in Asbestos-induced Mesotheliomas", Alba, Italy, September 7 - 10, **2005** (*could not attend due to family emergency*)

Invited Speaker, "Properties of Asbestos Involved in Mechanisms of Action Leading to Mesothelioma" Institute of Medicine: Asbestos: Selected Health Effects, National Academy of Sciences, Washington, DC, October 5, **2005**

Program Chair, 8<sup>th</sup> International Meeting on "Mechanisms of Action of Inhaled Particles and Nanoparticles", Research Triangle Park, NC, October 26 - 28, **2005**

Invited Speaker, Department of Thoracic Surgery, "Inhibition of Cell Signaling Pathways in Mesothelioma", Brigham and Women's Hospital, Boston, MA, December 9, **2005**

Invited Speaker, "Screening Assays for Cell Signaling by Particles", 1<sup>st</sup> International Conference on "Nanotechnology: Biomedical Aspects", Miami, FL, January 30 - February 3, **2006**

Session Chair, Experimental Biology 2006 Symposium on "Molecular and Cellular Basis of Disease: Redox Mediated Diseases, San Francisco, CA, April 4, **2006**

Invited Speaker, "Protein Kinase C Signaling by Asbestos is Critical to Cell Injury, Transcription of Matrix Metalloproteinases and Pulmonary Fibrosis", Department of Pathobiology, Brown University, Providence, RI, May 4, **2006**

Invited Speaker, "Cell Signaling in Mesothelioma", 8<sup>th</sup> International Conference of the International Mesothelioma Interest Group, Chicago, IL, October 19, **2006**

Faculty Member, "Mechanisms of Mesothelioma", Mesothelioma Applied Research Foundation, Chicago, IL, October 20, **2006**

Program Committee Member and Session Co-Chair, "Physiological Genomics and Proteomics of Lung Disease", American Physiological Society Conference, Fort Lauderdale, FL, November 2 - 5, **2006**

Invited Speaker, "Cell Signaling in Asbestos-Related Diseases", Symposium on "Interactions among Infectious Agents, Environmental Carcinogens & Genetics in Human Cancer Development", John A. Burns School of Medicine and Cancer Center of Hawaii, Honolulu, Hawaii, February 16, **2007**

Invited Speaker, "Oxidant Injury in Lung Disease", Gordon Conference on "Oxidative Stress in Disease", Ventura, CA, March 11 - 15, **2007**

Invited Participant, International Council on Nanotechnology Conference "Towards Predicting Nano-Bio Interactions, Zurich, Switzerland, June 5 - 7, **2007** (*declined due to schedule conflict*)

Invited Speaker, "Gene Profiling and Approaches for Therapy of Mesothelioma Using Nanoporous Spheres", ESF-EMBO Symposium on Probing Interactions between Nanoparticles, Biomaterials and Biological Systems - Alternative Approaches to Bio- and Nano-toxicity, Sant Feliu de Guixols, Spain, November 3 - 8, **2007**

Plenary Speaker, "Asbestos and Cell Signaling", 1<sup>st</sup> Asian Conference on Environmental Mutagens and 36<sup>th</sup> Annual Meeting of the Japanese Environmental Mutagen Society, Kitakyushu, Japan, November 29 - 30, **2007**

Organizing Committee, 9<sup>th</sup> International Conference on Particles: Risks and Opportunities, Cape Town, South Africa, September 2 - 5, **2008**

Faculty and Invited Session Chair, 9<sup>th</sup> International Conference of the International Mesothelioma Interest Group, Amsterdam, The Netherlands, September 26 - 28, **2008**

Invited Speaker, "Current Perspectives on the Pathogenesis of Mesothelioma", XXVII<sup>th</sup> International Academy of Pathology Congress, Athens, Greece, October 12 - 17, **2008**

Invited Speaker, "Microparticles for Release of Chemotherapeutic Drugs and si Constructs in Therapy of Mesotheliomas", 2<sup>nd</sup> NIH Mesothelioma Conference, Washington, DC, March 6, **2009**

Invited Speaker, "Cell Signaling and Therapies for Mesothelioma", Lung Biology Group, Dartmouth Medical School, Hanover, NH, May 6, **2009**

Invited Speaker, "Use of *In Vitro* and Inhalation Models for Assessment of Nanoparticle Effects on Lung Cells", VII<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Science, Rome, Italy, August 30 - September 3, **2009**

Invited Speaker, "The Inflammasome in Asbestos-related Diseases", 4<sup>th</sup> International Conference on Oxidative/Nitrosative Stress and Disease, New York Academy of Sciences, New York, NY, October 28 - 30, **2009**

Speaker, "Targeting the Inflammasome in Mesothelioma Using Anakinra", International Symposium on Malignant Mesothelioma 2010, Mesothelioma Applied Research Foundation (MARF), Washington, DC, June 10 - 12, **2010**

Invited Speaker, "Inflammation and Asbestos-induced Diseases", Annual Meeting of the American Chemical Society, Boston, MA, August 25, **2010**

Invited Speaker, "Chronic Inflammation and Mesothelioma", American Association of Cancer Research/ American Chemical Society Conference on Chemistry and Cancer Research: The Biological Chemistry of Inflammation as a Cause of Cancer, January 30 - February 2, **2011**

Invited Speaker, "Targeting the Inflammasome in Asbestos-related Diseases", 50<sup>th</sup> Annual Meeting of the Society of Toxicology, Washington, DC, March 13 - 15, **2011**

Invited Presenter, 1<sup>st</sup> Annual Libby Amphibole Symposium, October 13 - 14, **2011**

Invited Session Chair and Speaker, "Dose Response Molecular Responses to Asbestos and Silica in Human Lung Cells", 11<sup>th</sup> Annual International Conference on Dose-Response 2012: Implications for Toxicology, Medicine and Risk Assessment, University of Massachusetts Amherst, Amherst, MA, April 24 - 25, **2012**

Invited Presenter and Session Chair, "ERK Signaling Pathways in Mesothelioma", 11<sup>th</sup> International Conference of the International Mesothelioma Interest Group, Boston, MA, September 11 - 14, **2012**

Invited Presenter and Panel Member, 2<sup>nd</sup> Annual Libby Amphibole Symposium, October 12, **2012**

Invited Presenter, Medalist lecture on "Cell Signaling Pathways in Mesothelioma", 12<sup>th</sup> International Conference of the International Mesothelioma Interest Group, Cape Town, South Africa, October 21 - 24, **2014** (*could not attend due to prior UVM commitment*)

Invited Speaker and Rapporteur, "Mechanistic Studies of EMPs: Cell Cultures, Organ Cultures and Beyond?" The Monticello Conference, Charlottesville, VA, October 16 - 19, **2017**

Invited Speaker and Moderator, "Asbestos in Talc", The Joint Institute of Food Safety and Applied Nutrition (JIFSAN), FDA, University of Maryland, MD, November 28, **2018**

**Refereed Manuscripts\*, Book Chapters, Monographs and Editorials (\*peer-reviewed)**

1. \*Sivak A, Mossman BT, and Van Duuren BL: Activation of cell membrane enzymes in the stimulation of cell division. *Biochem Biophys Res Comm* 46(2):605-609, **1972** PMID: 4333422

2. \*Mossman BT, Gray MJ, Silberman L, and Lipson RL: Identification of neoplastic versus normal cells in human cervical cell culture. *Am J Obstet Gynecol* 43(5):635-639, **1974** PMID: 4595695
3. Mossman BT and Craighead JE: Topical application of polycyclic hydrocarbons to differentiated respiratory epithelium in long-term organ cultures. In: Experimental Lung Cancer, (E Karbe and JF Park, eds.), Springer-Verlag, Berlin, Germany, 514-520, **1974**
4. \*Mossman BT and Craighead JE: Long-term maintenance of differentiated respiratory epithelium in organ culture. I. Medium composition. *Proc Soc Exp Biol Med* 149(1):227-233, **1975** PMID: 1144432
5. \*Mossman BT, Ley BW, and Craighead JE: Squamous metaplasia of the tracheal epithelium in organ culture. I. Effects of hydrocortisone and -retinyl acetate. *Exp Mol Pathol* 24(3):405-414, **1976** PMID: 1278337
6. \*Mossman BT, Kessler JB, Ley BW, and Craighead JE: Interaction of crocidolite asbestos with hamster respiratory mucosa in organ culture. *Lab Invest* 36(2):131-139, **1977** PMID: 839730
7. Mossman BT and Craighead JE: Organ culture of the hamster bladder epithelium. *Tissue Cult Assoc Man* 3:623-624, **1977**
8. Mossman BT: Autoradiography for determination of DNA synthesis in hamster bladder epithelium. *Tissue Cult Assoc Man* 3:663-666, **1977**
9. \*Mossman BT, Heintz N, MacPherson BV, and Craighead JE: Squamous metaplasia of the tracheal epithelium in organ culture. II. Nutritional influences. *Proc Soc Exp Biol Med* 157(3):500-505, **1978** PMID: 634992
10. \*Mossman BT and Craighead JE: Induction of neoplasms in hamster tracheal grafts with 3-methylcholanthrene-coated Lycra fibers. *Cancer Res* 38(11 Pt 1):3717-3722, **1978** PMID: 698931
11. \*Mossman BT, Adler KB, and Craighead JE: Interaction of carbon particles with tracheal epithelium in organ culture. *Environ Res* 16(1-3):110-122, **1978** PMID: 679909
12. \*Craighead JE and Mossman BT: Carcinoma induction by 3-methylcholanthrene in hamster tracheal tissue implanted in syngeneic animals. *Prog Exp Tumor Res* 24:48-60, **1979** PMID: 538263
13. Mossman BT and Craighead JE: Use of hamster tracheal organ cultures for assessing the cocarcinogenic effects of inorganic particulates on the respiratory epithelium. *Prog Exp Tumor Res* 24:37-47, **1979** PMID: 538256
14. \*Mossman BT, Craighead JE, and MacPherson BV: Asbestos-induced epithelial changes in organ cultures of hamster trachea: inhibition by retinyl methyl ether. *Science* 207(4428):311-313, **1980** PMID: 7350661
15. \*Craighead JE, Mossman BT, and Bradley BJ: Comparative studies on the cytotoxicity of amphibole and serpentine asbestos. *Environ Health Perspect* 34:37-46, **1980** PMID: 6993203; PMCID: PMC1568520
16. \*Last JA, Kaizu T, and Mossman BT: Glycoprotein synthesis by an established cell line from hamster tracheal epithelium. *Exp Lung Res* 1(2):89-98, **1980** PMID: 7227345
17. \*Mossman BT, Ezerman EB, Adler KB, and Craighead JE: Isolation and spontaneous transformation of cloned lines of hamster tracheal epithelial cells. *Cancer Res* 40(12):4403-4409, **1980** PMID: 7192176
18. Mossman BT: Use of tracheal organ cultures and grafts to explore the interactions of environmental particulates with respiratory epithelial cells. In: Topics in Environmental Pathology, (RB Hill and JA Terzian, eds.), Universities Associated for Research and Education in Pathology, Inc., Bethesda, MD, 89-, **1980**
19. Mossman BT, Adler KB, and Craighead JE: Cytotoxic and proliferative changes in tracheal organ cultures after exposure to mineral dusts. In: The In Vitro Effects of Mineral Dusts, (RC Brown, IP Gormley, M Chamberlain, R Davies, eds.) Academic Press, London, UK, 241-250, **1980**
20. \*Mossman BT and Craighead JE: Mechanisms of asbestos carcinogenesis. *Environ Res* 25(2):269-280, **1981** PMID: 7023937
21. \*Eastman A, Mossman BT, and Bresnick E: Formation and removal of benzo(a)pyrene adducts of DNA in hamster tracheal epithelial cells. *Cancer Res* 41(7):2605-2610, **1981** PMID: 6265063
22. \*Woodworth CD, Mossman BT, and Craighead JE: Comparative effects of fibrous and nonfibrous minerals on cells and liposomes. *Environ Res* 27(1):190-205, **1982** PMID: 6279387
23. Mossman BT, Adler KB, Jean L, and Craighead JE: Mechanisms of hypersecretion in rodent tracheal explants after exposure to chrysotile asbestos. Studies using lectins. *Chest* 81(5):23S-24S, **1982**
24. \*Landesman JM and Mossman BT: Induction of ornithine decarboxylase in hamster tracheal epithelial

- cells exposed to asbestos and 12-O-tetradecanoylphorbol-13 acetate. *Cancer Res* 42(9):3669-3675, **1982** PMID: 6286111
25. \*Eastman A, Mossman BT, and Bresnick E: Modulation of the interaction of benzo(a)pyrene with a hamster tracheal epithelial cell line. *Carcinogenesis* 3(11):1283-1287, **1982** PMID: 6983932
26. \*Craighead JE and Mossman BT: The pathogenesis of asbestos-associated diseases. *N Engl J Med* 306(24):1446-1455, **1982** PMID: 7043267
27. Mossman BT and Craighead JE: Comparative cocarcinogenic effects of crocidolite asbestos, hematite, kaolin, and carbon in implanted tracheal organ cultures. *Ann Occup Hyg* 26(1-4):553-567 **1982** PMID: 6295246
28. Mossman BT: Mechanisms of asbestos-induced carcinogenesis in hamster trachea. Proceedings of the 12<sup>th</sup> Conference on Environmental Toxicology, Report #AFAMRL-TR-81-149, Aerospace Medical Research Laboratory, 1, **1982**
29. Mossman BT and Craighead JE: Mechanisms of asbestos and nonasbestiform particles and fibers in bronchogenic carcinoma. In: Health Issues Related to Metal and Nonmetallic Mining, (WL Wagner, WN Rom, and JA Merchants, eds.), Butterworth Publishers, Boston, MA, 123-134, **1983**
30. \*Mossman BT, Jean L, and Landesman JM: Studies using lectins to determine mineral interaction with cellular membranes. *Environ Health Perspect* 51:23-25, **1983** PMID: 6315363; PMCID: PMC1569312
31. \*Woodworth C, Mossman BT, and Craighead JE: Interaction of asbestos with metaplastic squamous epithelium developing in organ cultures of hamster trachea. *Environ Health Perspect* 51:27-33, **1983** PMID: 6315370; PMCID: PMC1569289
32. \*Mossman BT, Eastman A, Landesman JM, and Bresnick E: Effects of crocidolite and chrysotile asbestos on cellular uptake and metabolism of benzo(a)pyrene in hamster tracheal epithelial cells. *Environ Health Perspect* 51:331-335, **1983** PMID: 6315375; PMCID: PMC1569314
33. Mossman BT and Landesman JM: Importance of oxygen free radicals in asbestos-induced injury to airway epithelial cells. *Chest* 83(5 Suppl):50S-51S, **1983** PMID: 6839851
34. Mossman BT, Light W, and Wei E: Asbestos: mechanisms of toxicity and carcinogenicity in the respiratory tract. *Annu Rev Pharmacol Toxicol* 23:595-615, **1983** PMID: 6347054
35. \*Wilson GL, Mossman BT, and Craighead JE: Use of pancreatic beta cells in culture to identify diabetogenic N-nitroso compounds. *In Vitro* 19:25-30, **1983** PMID: 6218070
36. \*Eastman A, Mossman BT, and Bresnick E: Influence of asbestos on the uptake of benzo(a)pyrene and DNA alkylation in hamster tracheal epithelial cells. *Cancer Res* 43(3):1251-1255, **1983** PMID: 6297722
37. \*Woodworth CD, Mossman BT, and Craighead JE: Squamous metaplasia of the respiratory tract. Possible pathogenic role in asbestos-associated bronchogenic carcinoma. *Lab Invest* 48:578-584, **1983** PMID: 6843088
38. \*Woodworth CD, Mossman BT, and Craighead JE: Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. *Cancer Res* 43(10):4906-4912, **1983** PMID: 6883341
39. \*Mossman BT: *In vitro* approaches for determining mechanisms of toxicity and carcinogenicity by asbestos in the gastrointestinal and respiratory tracts. *Environ Health Perspect* 53:155-161, **1983** PMID: 6363051; PMCID: PMC1569089
40. \*Craighead JE, Adler KB, Butler GB, Emerson RJ, Mossman BT, and Woodworth CD: Health effects of Mount St. Helens volcanic dust. *Lab Invest* 48:5-12, **1983** PMID: 6823090
41. \*Mossman BT, Eastman A, and Bresnick E: Asbestos and benzo(a)pyrene act synergistically to induce squamous metaplasia and incorporation of [<sup>3</sup>H]thymidine in hamster tracheal epithelium. *Carcinogenesis* 5(11):1401-1404, **1984** PMID: 6488462
42. \*Adler KB, Mossman BT, Butler GB, Jean LM, and Craighead JE: Interaction of Mount St. Helens' volcanic ash with cells of the respiratory epithelium. *Environ Res* 35(2):346-361, **1984** PMID: 6510386
43. \*Wilson GL, Patton NJ, McCord JM, Mullins DW, and Mossman BT: Mechanisms of streptozotocin- and Jeanalloxan-induced damage in rat B cells. *Diabetologia* 27(6):587-591, **1984** PMID: 6241574
44. \*Bernacki RJ, Wilson GL, Mossman BT, Angelino N, Kanter PM, and Korytnyk W: The therapeutic and diabetogenic potential of two newly synthesized nitrosoureido sugars. *Cancer Res* 45(2):695-702, **1985** PMID: 3881170
45. Mossman BT and Marsh JP: Mechanisms of toxic injury by asbestos fibers: role of oxygen-free radicals.



- In: *In Vitro Effects of Mineral Dusts*, 3<sup>rd</sup> International Workshop, (EE Beck and J Bignon, eds.), NATO ASI Series, Springer-Verlag, Berlin, Germany 66-74, **1985**
46. Fisher GL, Mossman BT, McNeill K, Marsh JP, McFarland AR and Hart RW: Investigations into the mechanisms of asbestos toxicity. In: *In Vitro Effects of Mineral Dusts*, 3<sup>rd</sup> International Workshop, (EE Beck and J Bignon, eds.), NATO ASI Series, Springer-Verlag, Berlin, Germany, 31-38, **1985**
  47. Marsh JP, Jean L, and Mossman BT: Asbestos and fibrous glass induce biosynthesis of polyamines in tracheobronchial epithelial cells *in vitro*. In: *In Vitro Effects of Mineral Dusts*, 3<sup>rd</sup> International Workshop, (EE Beck and J Bignon, eds.), NATO ASI Series, Springer-Verlag, Berlin, Germany, 305-311, **1985**
  48. Mossman BT, Cameron GS, and Yotti LP: Cocarcinogenic and tumor promoting properties of asbestos and other minerals in tracheobronchial epithelium. In: *Cancer: A Comprehensive Survey* (Cancer of the Respiratory Tract, Predisposing Factors, Vol. 8), (MJ Mass, DG Kaufman, JM Siegfried, VE Stede, S Nesnow, eds.), Raven Press, New York, NY, 217-238, **1985**
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315. Mossman BT and Puglioni A: *In vitro* biological activity and mechanisms of carcinogenic diseases induced by mineral fibres. In: Mineral Fibres: Crystal Chemistry, Chemical and Physical Properties, Biological Interaction and Toxicity. (AF Gualtieri, Ed.) EMU Notes in Mineralogy, Vol. 18, Ch. 8, pp. 261-307, **2017**
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319. \* Mossman BT: Mechanistic *In Vitro* studies: what they have told us about carcinogenic properties of elongated mineral particles (EMPs). *Toxicol Appl Pharm* doi: 10.1016/j.taap.2018.07.018

#### **Books/Series Editor**

1. BT Mossman and RO Begin, eds.: Effects of Mineral Dusts on Cells, NATO ASI Series H: Cell Biology, Springer-Verlag, Berlin, Germany, pp.1-470, **1989**
2. GD Guthrie Jr. and BT Mossman, eds.: Health Effects of Mineral Dusts, Reviews in Mineralogy, Vol. 28 (Series Editor: Paul H. Ribbe), Mineralogical Society of America, Washington, DC, pp. 1-584, **1993**
3. BT Mossman (Guest Editor): Forum on "Signal transduction by oxidants: Look who's talking". *Free Radic Biol Med* 28(9):1315-1316, **2000** PMID: 10924850
4. DJ Taatjes and BT Mossman, eds.: Cell Imaging Techniques: Methods and Protocols (Methods in Molecular Biology, Vol. 319), Humana Press, Totowa, NJ, pp. 1-490, **2006**

#### **Research Support**

NIH NIOSH (09/01/1978 - 08/31/1982) "Carcinogenic Mechanisms of Asbestos", Total \$397,899; PI - 50% FTE  
 NIH NIAM (07/01/1979 - 06/30/1982) "Establishment of Insulin-secreting Cell Lines", Total \$101,980; PI - 30% FTE (Young Investigator Grant)  
 NIH NCI (07/01/1982 - 08/30/1985) "Role of Minerals as Co-factors in Bronchogenic Carcinoma", Total \$350,132, first year \$108,444; PI - 30% FTE  
 Parker B. Francis Foundation (07/01/1982 - 06/30/1985) Post-doctoral fellowship - Maria A. Shatos, Total \$63,174, first year \$20,566; Program Director  
 ADA (08/01/1982 - 07/30/1984) "Diabetogenic Chemicals: Mechanisms of Tropism for and Damage to Pancreatic Beta Cells", Total \$49,877, first year \$24,607; PI - 15% FTE (returned 02/01/1983 because of over commitments)

American Cancer Society, Institutional Research Award (09/01/1982 - 08/31/1983) "Comparative Interactions of Methylnitrosourea with the DNA of Pancreatic Beta Cells and Fibroblasts", Total \$7,500; PI - 5% FTE

American Cancer Society (01/01/1983 - 12/31/1985) "Fiber-cell Interaction in Bronchogenic Carcinoma", Total \$332,280, first year \$98,444; PI - 30% FTE

NIH NIEHS (02/01/1983 - 01/31/1986) "N-nitroso Compounds: Mechanisms of Damage to Beta Cells", Total \$327,306, first year \$96,283; PI - 20% FTE

NIH NCI (09/01/1985 - 08/30/1988) "Oxygen Radicals in Mineral Damage/Tumor Promotion", Total \$347,508, first year \$106,580; PI - 30% FTE

NIH NIEHS (02/01/1986 - 01/31/1989) "Preventive Approaches to Mineral-induced Fibrosis", Total \$328,339, first year \$104,355; PI - 50% FTE

NHLBI (12/01/1986 - 11/30/1991) Pulmonary SCOR - Occupational and Immunologic Lung Disease, Director Project 05, "Preventive approaches to asbestosis", ADC \$62,656; 15% FTE

NATO Advanced Research Workshop grant (07/01/1988 - 12/30/1988) "Effects of Mineral Dusts on Cells", Total \$22,500

NIH NHLBI/NIEHS/NCI (09/01/1988 - 08/31/1989) Conference grant, "Workshop on Effects of Mineral Dusts on Cells", Total \$28,000

American Cancer Society (06/01/1989 - 06/30/1990) Fellowship for Susan Edmondson, Total \$1,200

Howard Hughes Helix Award (01/01/1990 - 12/31/1990) Undergraduate support for Kaaren Haldeman, TDC \$800

EPA (09/01/1991 - 12/31/1994) "Lung Defense Mechanisms after Occupational and Environmental Exposure to Asbestos", first year \$150,000, TDC \$450,422; PI - 15% FTE

NIH NHLBI (04/01/1993 - 03/30/1997) "Molecular Biology of Lung Antioxidant Enzyme Regulation", ADC \$168,887; PI - 40% FTE

NIH (09/01/1993 - 08/31/1998) "Mechanisms of Cell Replication in Asbestos Cancers", ADC \$138,570; PI - 38% FTE

NIH NIEHS (02/01/1994 - 01/31/1999) "Asbestos-Induced Oxidative DNA Damage and Repair", ADC \$44,239; Subcontract - Bennett Van Houten PI

NIH NIOSH (10/01/1994 - 09/30/1997) "Stress Genes as Biomarkers of Mineral Dust Exposure", Advisor to Dr. Cynthia R. Timblin for Special Emphasis Career Development Award, ADC \$50,000

Parker B Francis Foundation (07/01/1995 - 06/30/1998) "Molecular Pathways of Proliferation and Inflammation Activated in Lung Epithelial Cells by Reactive Oxygen and Nitrogen Species", ADC \$29,875; Yvonne Janssen PI

NIH (08/01/1996 - 07/31/2000) "The Nature of Lung Antioxidant Defense Mechanisms", ADC \$25,505; Subcontract - Ye-Shih Ho, PI

NIH (09/30/1997 - 09/29/2001) "EGFR Signaling Pathways by Particulates in Lung Disease", ADC \$183,546; PI - 30% FTE

NIH (06/01/1998 - 05/30/2001) "Molecular Signaling by Oxidant Stress in Lung Epithelium", ADC \$185,728; PI - 35% FTE

NIH (08/15/1998 - 07/31/2002) "Asbestos and NO<sub>2</sub> in Environmental Lung Disease", ADC \$189,648; Nicholas H. Heintz PI

NIH (11/19/1998 - 11/23/1998), 1998 Oxygen Society Meeting Conference Grant, TDC \$39,928

NHLBI (09/01/2005 - 08/31/2006), 8<sup>th</sup> International Meeting on "Mechanisms of Action of Inhaled Fibers, Particles and Nanoparticles", ADC \$30,000; PI - 0% FTE

NIH P01 HL67004/01-05 (06/01/2001 - 04/30/2006; NCE - 04/30/2007) "Signaling in Epithelial Injury, Proliferation and Fibrosis", Total project ADC: \$1,049,247; PD: Project 1, "MAPK Signaling in Injury, Proliferation & Fibrosis", ADC: \$167,351; PL - 25% FTE: Project 3, "Protein Kinase C and MAPK in Epithelial Responses", ADC: \$191,711; Co-I - 15% FTE: Core A, "Administrative Core", ADC: \$85,513; CL - 10% FTE

NIH NIEHS R01 ES10638-01 (08/08/2003 - 07/31/2007) "Molecular Regulation of Transcriptional Competence by Metals", ADC \$86,915; Aaron Barchowsky PI (University of Pittsburgh)

NCI K01 CA104159 (05/01/2004 - 04/30/2008) "Role of Fra-1 in Mesothelioma", ADC: \$129,415 Maria E. Ramos-Nino PI

MARF (01/01/2007 - 12/31/2008; NCE - 12/31/2009) "Nanoporous Spheres for Chemotherapeutic Drug Delivery in Mesothelioma Patients", ADC: \$50,000; PI - 5% FTE

NIH NCI R01 CA106567 (04/01/2005 - 03/31/2010) "Role of Inflammatory Mediators in Asbestos and Simian Virus (SV40) Carcinogenesis", ADC: \$19,750 (Subcontract); Michele Carbone, PD (University of Hawaii), Co-I - 3% FTE

NIH 1R41 CA12615501 (09/27/2007 - 07/31/2010) "Improving the Transfer of ERK siRNA Constructs Using Nanoporous Silica", ADC: \$94,503; Christopher C. Landry PI, Co-I - 2% FTE

Eurotalc/Industrial Minerals Association (11/01/2005 - 10/31/2010) "Comparative Effects of Nonasbestiform Talc and Asbestos on Gene Profiles and Proliferation/Cell Death in Human Pleural Mesothelial and Ovarian Epithelial Cells *in Vitro*", TDC: \$90,000, PI (This project did not result in any salary support for the PI)

NIH NIEHS RC1 ES018053-01 (10/01/2009 - 07/31/2011) "Mechanisms for Cardiovascular Effects of Air Pollutants: Effect of Age and Sex", ADC: \$332,223; Naomi K. Fukagawa PI, Co-I - 5% FTE

NCI P01 CA11407 (08/01/2006 - 08/31/2011) "Pathogenesis of Mesothelioma"; Project 2 Leader, "ERK Pathways in Pathogenesis and Chemoresistance of Mesothelioma", ADC: \$206,512 (Subcontract); Michele Carbone, PD (University of Hawaii), Co-I - 25% FTE

NIH/NIEHS T32 ES007122 (07/01/1982 - 06/30/2013) "Environmental Pathology Training Grant" (Director), TDC \$2,500,000 for a five-year period. The major goal of this project is to provide graduate training in environmental pathology. Six pre-doctoral and three post-doctoral positions are funded annually. PI - 10% FTE

Research (2010-2016) on silica and silicosis was supported by an unrestricted grant from the Weijerhorst Foundation in collaboration with researchers at the University of Maastricht, The Netherlands.

NIEHS (2016) R13 Conference grant for support of junior/underrepresented minorities for attendance at the 11th International Particles/Toxicology Conference"; Singapore, Co-PI (no salary support) Gunter Oberdorster, PI.

DOD (09/01/2014-8/31/2016) "Exosomes in Development and Therapy of Malignant Mesothelioma", Total \$300,000; Co PI- 4% FTE (1 year non-funded extension- 8/31/2017).

# Exhibit B



Brooke T. Mossman, M.S., Ph.D.

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IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF NEW JERSEY

- - -

IN RE: JOHNSON & :  
JOHNSON TALCUM POWDER :  
PRODUCTS MARKETING, :  
SALES PRACTICES, AND : NO. 16-2738  
PRODUCTS LIABILITY : (FLW) (LHG)  
LITIGATION :  
:  
THIS DOCUMENT RELATES :  
TO ALL CASES :

- - -

April 8, 2019

- - -

Videotaped deposition of  
BROOKE T. MOSSMAN, M.S., Ph.D., taken  
pursuant to notice, was held at Hotel  
Vermont, 41 Cherry Street, Burlington,  
Vermont, beginning at 9:12 a.m., on the  
above date, before Michelle L. Gray, a  
Registered Professional Reporter,  
Certified Shorthand Reporter, Certified  
Realtime Reporter, and Notary Public.

- - -

GOLKOW LITIGATION SERVICES  
877.370.3377 ph | 917.591.5672 fax  
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Brooke T. Mossman, M.S., Ph.D.

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THE VIDEOGRAPHER: We are now on the record. My name is Dan Lawlor. I'm a videographer with Golkow Litigation Services. Today's date is April 8th, 2019. And the time is 9:12 a.m.

This video deposition is being held in Burlington, Vermont, in the matter of talcum powder litigation, MDL Number 2738.

Counsel will be noted on the stenographic record.

The deponent today is Brooke Mossman, Ph.D.

The court reporter is Michelle Gray and will now swear in the witness.

- - -

... BROOKE T. MOSSMAN, M.S., Ph.D., having been first duly sworn, was examined and testified as follows:

- - -

THE VIDEOGRAPHER: Please

4 (Pages 10 to 13)

Brooke T. Mossman, M.S., Ph.D.

<p style="text-align: right;">Page 14</p> <p>1 proceed.</p> <p>2 - - -</p> <p>3 EXAMINATION</p> <p>4 - - -</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Good morning.</p> <p>7 A. Good morning.</p> <p>8 Q. How are you, Dr. Mossman?</p> <p>9 A. Fine, thank you.</p> <p>10 Q. We spoke on the phone on the</p> <p>11 Brower case; is that correct?</p> <p>12 A. We did.</p> <p>13 Q. And I have some questions</p> <p>14 for you here today. First thing is, I</p> <p>15 want to just attach, for reference, is</p> <p>16 the notice of your deposition, I'm going</p> <p>17 to attach as Exhibit 1.</p> <p>18 Have you -- have you seen</p> <p>19 this notice of deposition?</p> <p>20 A. I haven't.</p> <p>21 Q. All right.</p> <p>22 (Document marked for</p> <p>23 identification as Exhibit</p> <p>24 Mossman-1.)</p>	<p style="text-align: right;">Page 16</p> <p>1 to attach that as Exhibit 2.</p> <p>2 (Document marked for</p> <p>3 identification as Exhibit</p> <p>4 Mossman-2.)</p> <p>5 BY MR. SMITH:</p> <p>6 Q. I also was provided some</p> <p>7 supplemental -- I saw the materials that</p> <p>8 you considered that were attached to your</p> <p>9 report. And I was also provided</p> <p>10 supplemental materials considered. Are</p> <p>11 these additional materials that you</p> <p>12 considered in this case, besides the ones</p> <p>13 that are included in your report?</p> <p>14 A. Yes.</p> <p>15 MR. SMITH: I'll attach that</p> <p>16 as Exhibit 3.</p> <p>17 (Document marked for</p> <p>18 identification as Exhibit</p> <p>19 Mossman-3.)</p> <p>20 BY MR. SMITH:</p> <p>21 Q. And we'll go over your</p> <p>22 report in more detail in a little bit.</p> <p>23 Please state your name and</p> <p>24 occupation.</p>
<p style="text-align: right;">Page 15</p> <p>1 BY MR. SMITH:</p> <p>2 Q. Okay. All right. And</p> <p>3 pursuant to your notice of your</p> <p>4 deposition, your counsel provided some</p> <p>5 invoices. Did you provide those to your</p> <p>6 counsel for your time?</p> <p>7 A. My -- my assistant did.</p> <p>8 Yes.</p> <p>9 Q. And I have one bill that</p> <p>10 totals \$16,548. I have another bill that</p> <p>11 totals \$30,626. And then I have a third</p> <p>12 bill which totals \$27,151 -- wait --</p> <p>13 yeah, \$151.41.</p> <p>14 Is that -- or do these three</p> <p>15 bills constitute all of the time that you</p> <p>16 have billed in this case?</p> <p>17 A. It may not have accounted</p> <p>18 for my time in the last week or two. I'm</p> <p>19 not sure when these were sent out.</p> <p>20 Q. Absent your time in the past</p> <p>21 couple of weeks, would this cover the</p> <p>22 bills that you have billed in this case?</p> <p>23 A. I believe so, yes.</p> <p>24 MR. SMITH: Okay. I'm going</p>	<p style="text-align: right;">Page 17</p> <p>1 A. Brooke Taylor Mossman. I'm</p> <p>2 a university distinguished professor in</p> <p>3 the department of pathology.</p> <p>4 Q. Are you retired?</p> <p>5 A. Semi-retired, yes.</p> <p>6 Q. What does that mean?</p> <p>7 A. What it means is that I have</p> <p>8 an office at the university. I have some</p> <p>9 responsibilities through my office at the</p> <p>10 university, but am not being paid</p> <p>11 formally by the university anymore.</p> <p>12 Q. And your professional title</p> <p>13 is that of an experimental pathologist,</p> <p>14 correct?</p> <p>15 A. My professional title is a</p> <p>16 professor of pathology and laboratory</p> <p>17 medicine.</p> <p>18 Q. You were trained in lung</p> <p>19 pathology and disease associated with</p> <p>20 asbestos exposure; is that correct?</p> <p>21 A. That's correct.</p> <p>22 Q. And you do not have any</p> <p>23 prior training in ovarian cancer; is that</p> <p>24 correct?</p>

5 (Pages 14 to 17)



Brooke T. Mossman, M.S., Ph.D.

<p style="text-align: right;">Page 18</p> <p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: Yeah. I 4 actually got a master's degree in 5 the department of obstetrics and 6 gynecology looking at cervical 7 cancer. 8 BY MR. SMITH: 9 Q. I'm talking about ovarian 10 cancer, ma'am. 11 A. I have not been trained in 12 ovarian cancer formally. 13 Q. You're not a medical doctor? 14 A. That's correct. 15 Q. And you also understand that 16 the issues involved in this case are not 17 that of cervical cancer but of ovarian 18 cancer? Do you understand that? 19 A. Yes, I do. 20 Q. You are not a diagnostic 21 pathologist, correct? 22 A. Correct. 23 Q. You're not an 24 epidemiologist, correct?</p>	<p style="text-align: right;">Page 20</p> <p>1 reproductive tract? 2 A. Yes, I've had formal courses 3 in my training on that. 4 Q. What formal courses of 5 training have you had on the female 6 reproductive tract? 7 A. I had a master's in 8 obstetrics and gynecology. And I had a 9 course -- actually it was an eight-credit 10 course which is a requirement for not 11 only the master's, but also medical 12 students who I took the course with. And 13 this covered anatomy of the entire body. 14 Q. So you had an eight-hour 15 course on human female anatomy? 16 A. No. An eight-hour course on 17 anatomy of every organ, of which female 18 anatomy was included. 19 MR. FROST: I object 20 belatedly to the form of that 21 question. 22 BY MR. SMITH: 23 Q. You are not a mineralogist; 24 is that correct?</p>
<p style="text-align: right;">Page 19</p> <p>1 A. No. But I am aware of the 2 epidemiological research which bolsters 3 my opinion in this case. 4 Q. Ma'am, are you an 5 epidemiologist? 6 A. I am not. 7 Q. You're not a gynecologist? 8 A. Correct. 9 Q. And you're not an 10 oncologist; is that correct? 11 A. Correct. 12 Q. You're not a gynecological 13 oncologist; is that correct? 14 A. That's correct. 15 Q. And you're not an expert in 16 anatomy and physiology; is that correct? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: Yeah, I have 20 been trained formally in medical 21 anatomy of the lung, yes. 22 BY MR. SMITH: 23 Q. How about of the rest of the 24 human body, such as the female</p>	<p style="text-align: right;">Page 21</p> <p>1 A. That's correct. 2 Q. You are not a geologist; is 3 that correct? 4 A. That's correct. 5 Q. You are not a materials 6 analyst; is that correct? 7 A. That's correct. 8 Q. Analyzing whether a sample 9 of material is talc, asbestos, or talc 10 with asbestos, you leave to the 11 mineralogists; is that correct? 12 A. That's correct. 13 Q. Same for determining if a 14 mineral is asbestos or asbestiform, you 15 would leave that to a mineralogist; is 16 that correct? 17 A. I would. 18 Q. You're not an expert in 19 determining the flexibility or rigidity 20 of asbestos or cleavage fragments; is 21 that correct? 22 A. That's correct. I don't 23 measure that. 24 Q. With regard to the</p>

6 (Pages 18 to 21)

Brooke T. Mossman, M.S., Ph.D.

<p style="text-align: right;">Page 22</p> <p>1 crystallinity of asbestos, cleavage 2 fragments, or talc, you are not an expert 3 in that area either, correct? 4 A. Correct. 5 Q. Same for surface properties. 6 You are not an expert in surface 7 properties of asbestos, cleavage 8 fragments, or talc; is that correct? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: I have 12 measured surface properties and 13 surface charge of materials in the 14 past. 15 BY MR. SMITH: 16 Q. Would you consider yourself 17 an expert in this area? 18 A. I think you have to clarify 19 what an expert in surface chemistry would 20 be. 21 Q. What would you define an 22 expert in surface chemistry to be? 23 A. I would describe that as 24 someone who has focused on an aspect of</p>	<p style="text-align: right;">Page 24</p> <p>1 BY MR. SMITH: 2 Q. Well, did you tell truthful 3 testimony in the Leavitt case in trial 4 and did you tell truthful testimony in 5 the Brower deposition? 6 A. Absolutely. 7 Q. Okay. So I can rely on that 8 testimony as being truthful, correct? 9 A. Yes. 10 Q. Okay. Thank you. 11 All right. If you'll look 12 at Page 83. 13 MR. FROST: You said 14 February 21? 15 MR. SMITH: Yep. 16 BY MR. SMITH: 17 Q. If you'll go to Line 8 and 18 it says, "Question: And similarly 19 surface properties of a particle, you 20 leave that to mineralogists as well, and 21 that's not an area within your expertise, 22 correct?" 23 And your answer was, "Again, 24 I should emphasize that one of the things</p>
<p style="text-align: right;">Page 23</p> <p>1 surface chemistry that's important. In 2 our case, we measured zeta potential or 3 surface charge of materials. 4 Q. Do you believe that your 5 work has -- that you are an expert in 6 this area because of your work in this 7 area? 8 A. I believe I'm an expert in 9 determining the surface charge of 10 materials that I have experimented with. 11 Q. Okay. Let's go to your 12 Leavitt deposition -- trial testimony, if 13 you wouldn't mind. It's on Page 83. And 14 it should be of the February session, 15 February 21st session. 16 Let me ask you this. Can I 17 rely on your prior trial testimony in the 18 Leavitt case and your prior deposition 19 testimony in the Brower case? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: Yeah, I'm not 23 sure what you mean, sir, in terms 24 of rely upon.</p>	<p style="text-align: right;">Page 25</p> <p>1 that we've done is looked at things such 2 as iron using this EDAX technique." 3 E-D-A-X. "So in that case, we have 4 looked at surface iron." 5 And question again: "Okay. 6 But other than looking at iron on the 7 surface of a particle, and we'll get into 8 that later, you determining surface 9 properties of a particular property of a 10 particular particle is not a matter 11 within your expertise, correct? 12 "I don't do that, yes, 13 that's correct." 14 Is that the correct answer? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yeah, surface 18 properties and surface charge are 19 two different things. Surface 20 charge being a subset of surface 21 properties. 22 So as I emphasize, I have 23 measured the surface charge of 24 materials, including talc, and</p>

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<p style="text-align: right;">Page 26</p> <p>1 that has been published.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Can I rely on your testimony</p> <p>4 that I just read in Leavitt as accurate</p> <p>5 and truthful?</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: In terms of</p> <p>9 iron, yes.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Thank you.</p> <p>12 Have you ever diagnosed or</p> <p>13 treated a person with mesothelioma?</p> <p>14 A. I have not.</p> <p>15 Q. Have you ever diagnosed or</p> <p>16 treated a person with ovarian cancer?</p> <p>17 A. I have not.</p> <p>18 Q. Have you ever been called</p> <p>19 upon to determine what caused a person's</p> <p>20 mesothelioma?</p> <p>21 A. You'll have to be a little</p> <p>22 more explicit. What do you mean by</p> <p>23 called upon?</p> <p>24 Q. Can you go to your Leavitt</p>	<p style="text-align: right;">Page 28</p> <p>1 Is that true?</p> <p>2 A. Yes.</p> <p>3 Q. And next question: "You've</p> <p>4 never been involved in the care and</p> <p>5 treatment of a person with mesothelioma,</p> <p>6 correct?"</p> <p>7 "I have not treated them,</p> <p>8 that's correct. I have been</p> <p>9 involved in studying drugs that</p> <p>10 help them though."</p> <p>11 Is that correct?</p> <p>12 A. That's correct.</p> <p>13 Q. Would the same be for a</p> <p>14 person that's been diagnosed with ovarian</p> <p>15 cancer, have you ever diagnosed or</p> <p>16 treated a person with ovarian cancer?</p> <p>17 A. I have not.</p> <p>18 Q. And you have not diagnosed a</p> <p>19 person with mesothelioma, correct?</p> <p>20 MR. FROST: Objection, asked</p> <p>21 and answered.</p> <p>22 THE WITNESS: Yeah.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. And you have never diagnosed</p>
<p style="text-align: right;">Page 27</p> <p>1 testimony Page 78.</p> <p>2 A. Mm-hmm.</p> <p>3 Q. It says, "Question: You</p> <p>4 have never diagnosed mesothelioma in a</p> <p>5 human being?</p> <p>6 "That's correct."</p> <p>7 Is that true?</p> <p>8 MR. FROST: I'm sorry,</p> <p>9 what -- where are you?</p> <p>10 THE WITNESS: Yeah, I'm --</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Page -- I'm sorry, Page 78,</p> <p>13 Line 11 through 13.</p> <p>14 MR. FROST: Okay.</p> <p>15 THE WITNESS: Okay.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. "Question: And you've never</p> <p>18 been diagnosed" -- "you've never" --</p> <p>19 excuse me.</p> <p>20 "Question: And you have</p> <p>21 never diagnosed mesothelioma in any human</p> <p>22 being, correct?"</p> <p>23 Your answer was, "That's</p> <p>24 correct."</p>	<p style="text-align: right;">Page 29</p> <p>1 a person with ovarian cancer, correct?</p> <p>2 MR. FROST: Same objection.</p> <p>3 THE WITNESS: That's</p> <p>4 correct.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. And the levels of exposure</p> <p>7 of each type of asbestos in terms of</p> <p>8 human risk are outside of your area of</p> <p>9 expertise; is that correct?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Yeah. You're</p> <p>13 going to have to be a little -- a</p> <p>14 little more specific on that. I</p> <p>15 don't --</p> <p>16 BY MR. SMITH:</p> <p>17 Q. Okay. Let's go to Leavitt</p> <p>18 testimony Page 92.</p> <p>19 All right. Starting on</p> <p>20 page -- excuse me, Page 92, Line 10.</p> <p>21 "Question: As then you can</p> <p>22 see on the next page and a half, the</p> <p>23 lawyer asked you about each type of</p> <p>24 asbestos, crocidolite, amosite,</p>

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<p style="text-align: right;">Page 30</p> <p>1 tremolite, actinolite, anthophyllite, 2 chrysotile. Did you see that?" 3 And your answer was, "I do." 4 "Question: And each time 5 you said that that was outside of your 6 area of expertise? 7 "Answer: Yes, the levels of 8 exposure of these in terms of human risk 9 are outside of my area of expertise." 10 Is that truthful testimony 11 and can I rely on that today? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah. That's 15 truthful, my statement is 16 truthful. 17 BY MR. SMITH: 18 Q. Thank you. 19 Is it important to 20 understand cancer development? 21 MR. FROST: Objection to 22 form. 23 MR. SMITH: What's the 24 matter with the form of the</p>	<p style="text-align: right;">Page 32</p> <p>1 A. I'm getting there. 2 Q. And if you'll focus in on 3 Line 14. 4 "Question: Is it important 5 to understand cancer development in your 6 opinion? 7 "Answer: Yes." 8 Can I rely on that testimony 9 as truthful? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Yes, it was a 13 very broad question, but in 14 general, yes, the answer's 15 correct. 16 BY MR. SMITH: 17 Q. Cell cultures or in vitro 18 studies are valuable in determining 19 mechanisms on cancer causation, correct? 20 A. Yes. They're part of the 21 hierarchy of studying different elements 22 of or models of cancer development. 23 Q. One way to determine if 24 biological mechanisms or pathways are</p>
<p style="text-align: right;">Page 31</p> <p>1 question? 2 MR. FROST: I don't 3 understand what you mean by 4 "important to understand cancer 5 development." 6 BY MR. SMITH: 7 Q. Do you understand what I 8 mean by "it's important to understand 9 cancer development," Doctor? 10 A. It -- it's very broad. 11 It's -- it's important for what? 12 Q. Let's go to your deposition 13 testimony in Brower. 14 A. Okay. 15 Q. You got that in front of 16 you, Doctor? 17 A. I -- I think that's Leavitt. 18 MR. FROST: I believe this 19 is it. October 26th. 20 It fell apart. 21 BY MR. SMITH: 22 Q. Page 49, Doctor. You there? 23 A. I am not yet, sorry. 24 Q. That's okay.</p>	<p style="text-align: right;">Page 33</p> <p>1 triggered is to conduct in vitro studies 2 of relevant cells of disease and exposure 3 to the questioned substance; is that 4 correct? 5 A. Yes. 6 Q. You would agree with me that 7 it is important to identify and, if 8 possible, eliminate substances that 9 increase human risk of contracting 10 cancer? 11 MR. FROST: Objection to 12 form. 13 MR. SMITH: What's the 14 matter with the form? 15 MR. FROST: Again, I think 16 it's very vague to identify 17 impossible -- or important to 18 identify impossible to eliminate 19 substances. Compound question. 20 It's also vague as to what you 21 mean by important. 22 BY MR. SMITH: 23 Q. Do you understand the 24 question, Doctor?</p>

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<p style="text-align: right;">Page 34</p> <p>1 A. I don't.</p> <p>2 Q. Why don't we go to your</p> <p>3 deposition testimony in Brower. Page 49.</p> <p>4 Question, Line 6: "I'm asking in</p> <p>5 general, is it important as a scientist</p> <p>6 to identify and, if possible, eliminate</p> <p>7 any substances, if possible, that</p> <p>8 increase the risk of ovarian -- excuse</p> <p>9 me -- of contracting cancer?"</p> <p>10 And your answer was, "Yes,</p> <p>11 in principle."</p> <p>12 Can I rely on that as</p> <p>13 truthful?</p> <p>14 A. Yes.</p> <p>15 MR. FROST: I'll also lodge</p> <p>16 the same question that Mr. Bishop</p> <p>17 lodged to that question in that</p> <p>18 deposition.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Chronic inflammation and</p> <p>21 oxidative stress are two mechanisms that</p> <p>22 promote tumor and cancer development in</p> <p>23 known carcinogens; is that correct?</p> <p>24 A. That is true with regard to</p>	<p style="text-align: right;">Page 36</p> <p>1 BY MR. SMITH:</p> <p>2 Q. I understand potency. And</p> <p>3 we talked about potency and how</p> <p>4 crocidolite is more potent than, say,</p> <p>5 chrysotile. And that's not what I'm</p> <p>6 talking about, Doctor.</p> <p>7 You would agree with me that</p> <p>8 all types of asbestos are carcinogenic to</p> <p>9 human beings, correct?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Not really. I</p> <p>13 wouldn't agree with you without</p> <p>14 qualifying that statement with</p> <p>15 regard to consideration -- for</p> <p>16 example, IARC does consider all</p> <p>17 types of asbestos as carcinogenic.</p> <p>18 But as a scientist, it</p> <p>19 depends upon the type of asbestos</p> <p>20 and the dose that determines</p> <p>21 whether or not it's a carcinogen.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. So you're saying that not</p> <p>24 all types of asbestos are carcinogenic to</p>
<p style="text-align: right;">Page 35</p> <p>1 certain types of asbestos, correct.</p> <p>2 Q. And other known carcinogens,</p> <p>3 correct?</p> <p>4 A. The only carcinogen in terms</p> <p>5 of chronic inflammation that I'm aware of</p> <p>6 has been cigarette smoke.</p> <p>7 Q. And we'll talk about chronic</p> <p>8 inflammation and oxidative stress later.</p> <p>9 But asbestos is a known carcinogen,</p> <p>10 correct?</p> <p>11 A. That, again, is a very broad</p> <p>12 statement. Asbestos types vary in their</p> <p>13 potency for cancer.</p> <p>14 Q. All types of asbestos,</p> <p>15 regardless of type, are human</p> <p>16 carcinogens, correct?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: Again, I want</p> <p>20 to emphasize that it's a hierarchy</p> <p>21 of effects, and it depends upon</p> <p>22 the tumors that you're talking</p> <p>23 about.</p> <p>24</p>	<p style="text-align: right;">Page 37</p> <p>1 human beings?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: I'm saying</p> <p>5 that there are many types of</p> <p>6 tumors in humans, that with regard</p> <p>7 to asbestos there are certain</p> <p>8 types that are associated with</p> <p>9 asbestos exposures at high</p> <p>10 concentrations.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. My question is just really</p> <p>13 more simple. I understand that you can</p> <p>14 have levels of exposure and potency of</p> <p>15 different types of asbestos. But do you</p> <p>16 consider crocidolite a human carcinogen?</p> <p>17 A. I do.</p> <p>18 Q. Do you consider chrysotile a</p> <p>19 human carcinogen?</p> <p>20 A. I do with regard to lung</p> <p>21 cancer. I think it's very questionable</p> <p>22 with regards to mesothelioma.</p> <p>23 Q. What about actinolite? Do</p> <p>24 you consider that a human carcinogen?</p>



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<p style="text-align: right;">Page 38</p> <p>1 MR. FROST: Object to form.  2 THE WITNESS: Yeah. I don't  3 think that there is any human data  4 available to classify actinolite  5 as a human carcinogen.  6 BY MR. SMITH:  7 Q. And IARC and NTP disagree  8 with your assessment on that, don't they?  9 MR. FROST: Objection to  10 form. Misstates document.  11 THE WITNESS: Yeah. Let me  12 just state that I think both  13 agencies would consider that there  14 are no data in humans on  15 actinolite to prove its  16 carcinogenicity.  17 BY MR. SMITH:  18 Q. There have been formal  19 statements by the national toxicology  20 program of the United States, and in a  21 monograph by IARC that say that all types  22 of asbestos are human carcinogens. You  23 know that, Doctor, correct?  24 A. I do.</p>	<p style="text-align: right;">Page 40</p> <p>1 disagree with NTP and IARC if they  2 classify all types of asbestos, every  3 single one of them, as a human  4 carcinogen, and you're telling me  5 actinolite, there's not data to support  6 it's a carcinogen? How are you not  7 disagreeing with the NTP and IARC on that  8 matter then?  9 MR. FROST: Objection to  10 form.  11 THE WITNESS: I don't  12 believe they have statements on  13 different types of asbestos such  14 as actinolite.  15 BY MR. SMITH:  16 Q. Okay. We'll go get to that  17 in a minute. Does -- do you consider  18 tremolite a human carcinogen?  19 MR. FROST: Objection to  20 form.  21 THE WITNESS: Again, it  22 depends on the type of tumor you  23 are talking about and the dose of  24 the material and the form.</p>
<p style="text-align: right;">Page 39</p> <p>1 MR. FROST: Objection to  2 form.  3 BY MR. SMITH:  4 Q. So --  5 A. But that -- but let me just  6 emphasize here that lumping asbestos into  7 one category has been necessary in terms  8 of risk assessment, but in terms of  9 biological effects, that statement may  10 not be true, especially in humans.  11 Q. So you disagree with the  12 assessment of the national toxicology  13 program for the United States government  14 and IARC on this matter?  15 MR. FROST: Objection to  16 form. Misstates the document.  17 THE WITNESS: I don't  18 disagree. I'm just saying that  19 there are no data scientifically  20 to support the premise that  21 something like actinolite asbestos  22 is a human carcinogen.  23 BY MR. SMITH:  24 Q. Well, how do you not</p>	<p style="text-align: right;">Page 41</p> <p>1 BY MR. SMITH:  2 Q. Can it cause cancer in human  3 beings?  4 MR. FROST: Objection to  5 form.  6 THE WITNESS: If you're  7 talking about tremolite asbestos,  8 there is some data suggesting,  9 yes, that it can cause  10 mesothelioma.  11 BY MR. SMITH:  12 Q. What about anthophyllite?  13 MR. FROST: Same objection.  14 THE WITNESS: Yeah. A very  15 weak carcinogen compared to  16 crocidolite or amosite, certainly  17 in mesothelioma.  18 BY MR. SMITH:  19 Q. So you believe that all  20 types of asbestos are human carcinogens  21 except actinolite?  22 MR. FROST: Objection to  23 form. Misstates testimony.  24 THE WITNESS: No, that's not</p>

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<p style="text-align: right;">Page 42</p> <p>1 what I'm saying. I'm saying that</p> <p>2 if one looks at the scientific</p> <p>3 data on human population, there's</p> <p>4 not clear-cut information on the</p> <p>5 doses of certain materials such as</p> <p>6 tremolite, such as actinolite, in</p> <p>7 terms of carcinogenic effects.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. Again, back to my question.</p> <p>10 Chronic inflammation and oxidative stress</p> <p>11 are two mechanisms that promote tumor and</p> <p>12 cancer development in known carcinogens;</p> <p>13 is that correct?</p> <p>14 MR. FROST: Objection to</p> <p>15 form. Asked and answered.</p> <p>16 THE WITNESS: Yeah. I</p> <p>17 emphasize that that's known or</p> <p>18 certainly accepted for things such</p> <p>19 as asbestos, amphibole types of</p> <p>20 asbestos, as well as cigarette</p> <p>21 smoke.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Oxidants stimulate protein</p> <p>24 pathways that then cause the cell to</p>	<p style="text-align: right;">Page 44</p> <p>1 A. Those are pathways that</p> <p>2 we've studied, yes.</p> <p>3 Q. And you stated you do not</p> <p>4 need all of these factors to cause</p> <p>5 cancer; is that right?</p> <p>6 A. I think you need to be a</p> <p>7 little more explicit.</p> <p>8 Q. Well, let's look at your</p> <p>9 Leavitt testimony Page 133.</p> <p>10 A. Okay.</p> <p>11 Q. Let's see. Question on</p> <p>12 Line 8. "Now, you mention there were</p> <p>13 four different kinds, four different</p> <p>14 markers of asbestos, I mean of cancer.</p> <p>15 And asbestos causes all four of these</p> <p>16 markers to current cells?</p> <p>17 "Answer: Yes. And this</p> <p>18 gives you an idea of the different types</p> <p>19 of things we've studied. It's like the</p> <p>20 lock, and once that is unlocked, you get</p> <p>21 the development of cancer. And here we</p> <p>22 see where healthy cells become cancer</p> <p>23 cell and then that the cancer cell</p> <p>24 divides to become a malignant tumor.</p>
<p style="text-align: right;">Page 43</p> <p>1 transform and become a tumor, correct?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: That's some of</p> <p>5 the work that we've done, yes.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. And antioxidant --</p> <p>8 antioxidants are kicked in by a cell</p> <p>9 after exposure to low doses of an</p> <p>10 environmental agent as the doses become</p> <p>11 chronic or at higher concentration, the</p> <p>12 cells become overwhelmed and not able to</p> <p>13 correct the imbalance and then protein</p> <p>14 receptors on the cell are affected and</p> <p>15 cause the cell to transform; is that</p> <p>16 correct?</p> <p>17 A. That's true in some cases,</p> <p>18 yes.</p> <p>19 Q. And you talked about a</p> <p>20 four-step process to mesothelioma before,</p> <p>21 Doctor; is that correct, oxidant release,</p> <p>22 protein receptor changes, genome-wide</p> <p>23 expression changes and cell -- cell</p> <p>24 proliferation, correct?</p>	<p style="text-align: right;">Page 45</p> <p>1 "Let me ask you. If you</p> <p>2 only have three of the four markers, will</p> <p>3 you still have a mutation of that cell</p> <p>4 that causes cancer?</p> <p>5 "You may, but you won't have</p> <p>6 the entire process mimicked. So you need</p> <p>7 all four of these features of asbestos</p> <p>8 fibers to induce a cell, a healthy cell</p> <p>9 to become a malignant cell."</p> <p>10 Is that truthful testimony</p> <p>11 and can I rely on that?</p> <p>12 A. Yes, that's true.</p> <p>13 Q. Do you know which of these</p> <p>14 steps is necessary to cause ovarian</p> <p>15 cancer?</p> <p>16 A. No, I don't.</p> <p>17 Q. Of the four-step process you</p> <p>18 said to mesothelioma, and I'm going to</p> <p>19 refer to it like we did in Brower. Is it</p> <p>20 okay if I refer to the Shukla study by</p> <p>21 the first author Shukla, and then</p> <p>22 Hillegass by Hillegass? Is that fair?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. In the Shukla study</p>

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<p style="text-align: right;">Page 46</p> <p>1 you saw gene expression changes with talc 2 compared to neo mesothelial cells, 3 correct? 4 A. Could you repeat that again? 5 Q. Sure. In Shukla you saw 30 6 gene expression changes to talc compared 7 to neo mesothelial cells at the 8 75 micrometers per centimeter squared 9 concentration for eight hours, correct? 10 A. Yes. 11 Q. And -- but you never tested 12 talc in that study or in the Hillegass 13 study that came after it for oxidant 14 release, correct? 15 A. Could you repeat that again? 16 We've never tested cells for oxidant 17 release? 18 Q. In Hillegass, you did a 19 bunch of further studies on crocidolite 20 asbestos that you did not do on talc, 21 correct? 22 A. We only did additional 23 studies where we focused on the proteins 24 that were increased by asbestos. Many of</p>	<p style="text-align: right;">Page 48</p> <p>1 it was a transient change of gene 2 expression changes or not, fair? 3 MR. FROST: Objection to 4 form. 5 THE WITNESS: Yeah, we -- we 6 did not test asbestos or talc at 7 the highest concentration because 8 of cell death in the asbestos 9 exposed cultures. That's correct. 10 BY MR. SMITH: 11 Q. So you cannot tell me what 12 genes were altered or if they were more 13 altered at the higher concentration at 14 24 hours for talc that you saw at the 15 higher concentration at eight hours, 16 correct? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: We did not, 20 because they were -- I cannot tell 21 you that, because we didn't look 22 at talc for the reasons that I 23 just stated. 24 BY MR. SMITH:</p>
<p style="text-align: right;">Page 47</p> <p>1 these were not increased by talc. 2 Q. Ma'am, that's not my 3 question. 4 A. Okay. 5 Q. My question was, you did not 6 do all of the studies, all of those 7 assays and all of the protein 8 determination and all of that in 9 Hillegass. You did that for crocidolite 10 asbestos. You did not do talc in that 11 study? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah, and I 15 emphasize we didn't do talc, 16 because we didn't see that these 17 changes were protracted. 18 BY MR. SMITH: 19 Q. Well, ma'am, you did not 20 test talc at 24 hours at the higher 21 concentration -- 22 MR. FROST: Objection. 23 BY MR. SMITH: 24 Q. -- so you don't know whether</p>	<p style="text-align: right;">Page 49</p> <p>1 Q. And we'll talk more about 2 the studies in more detail in a minute. 3 In the Shukla study, you saw 4 the gene expression changes at eight 5 hours at the higher concentration 6 compared to -- compared to neo 7 mesothelial cells, correct? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: We saw 30 11 genes that were increased by 12 highest concentrations of talc. 13 BY MR. SMITH: 14 Q. But you never tested talc in 15 oxidant release of peritoneal mesothelial 16 cells in that study -- either one of 17 those studies, correct? 18 A. That's correct. 19 Q. And you did not test talc 20 for protein receptor changes in any of 21 those cells in either one of those 22 studies, correct? 23 A. We did -- 24 MR. FROST: Objection to</p>

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<p style="text-align: right;">Page 50</p> <p>1 form.</p> <p>2 THE WITNESS: Yeah, we</p> <p>3 didn't test talc because it didn't</p> <p>4 indicate genes that were increased</p> <p>5 that were related to oxidative</p> <p>6 stress, or the proteins that we</p> <p>7 were interested in that were</p> <p>8 increased by asbestos.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. You're telling me ATF3 and</p> <p>11 IL-8 are not associated of mediating</p> <p>12 inflammatory or oxidative processes in</p> <p>13 the cell?</p> <p>14 MR. FROST: Objection to</p> <p>15 form.</p> <p>16 THE WITNESS: ATF3 as we</p> <p>17 showed in the -- in the Shukla</p> <p>18 study is a gene that repairs cells</p> <p>19 from cytokine production.</p> <p>20 BY MR. SMITH:</p> <p>21 Q. Again, you did not test talc</p> <p>22 for protein receptor changes when applied</p> <p>23 to peritoneal mesothelial cells in either</p> <p>24 one of the two studies, correct?</p>	<p style="text-align: right;">Page 52</p> <p>1 you read that again?</p> <p>2 MR. FROST: Yeah, I was</p> <p>3 going to say, do you mind</p> <p>4 repeating that one?</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Sure.</p> <p>7 Protein receptors have</p> <p>8 chains that bind to cellular DNA, causing</p> <p>9 changes to genes in the DNA to create an</p> <p>10 abnormal cell which can lead to cancer,</p> <p>11 correct?</p> <p>12 A. That can be one endpoint of</p> <p>13 a protein receptor.</p> <p>14 Q. And there's a test for that,</p> <p>15 correct, a test to see which genes are</p> <p>16 upregulated or downregulated, correct?</p> <p>17 A. Genes but not proteins.</p> <p>18 Q. Correct. Cell proliferation</p> <p>19 is a hallmark of cancer causing</p> <p>20 substances and there are tools to look at</p> <p>21 cell division and assays to look at</p> <p>22 clumps of cells to see if they survive</p> <p>23 and become uncontrolled and lead to</p> <p>24 cancer; is that correct?</p>
<p style="text-align: right;">Page 51</p> <p>1 A. We didn't test anything for</p> <p>2 protein receptor changes in either of</p> <p>3 those studies. We were interested in</p> <p>4 gene expression.</p> <p>5 Q. And for talc in either one</p> <p>6 of those studies regarding peritoneal</p> <p>7 mesothelial cells, you did not check for</p> <p>8 cell proliferation, correct?</p> <p>9 A. Yes, we did not see genes</p> <p>10 that were indicative of cell</p> <p>11 proliferation by talc -- and we didn't</p> <p>12 test --</p> <p>13 Q. Did you test for gene -- did</p> <p>14 you test?</p> <p>15 A. No, we didn't see changes</p> <p>16 that were indicated at the gene level.</p> <p>17 Q. Protein receptors that have</p> <p>18 chains that bind to cellular DNA causing</p> <p>19 changes to genes in the DNA to create</p> <p>20 abnormal cell -- cells which can lead to</p> <p>21 cancer; is that correct?</p> <p>22 MR. FROST: Objection to</p> <p>23 form.</p> <p>24 THE WITNESS: Yeah, could</p>	<p style="text-align: right;">Page 53</p> <p>1 MR. FROST: Objection to</p> <p>2 form.</p> <p>3 THE WITNESS: Yeah, can we</p> <p>4 go through that piece by piece?</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Sure. Is cell proliferation</p> <p>7 a hallmark of cancer-causing substances?</p> <p>8 MR. FROST: Objection to</p> <p>9 form.</p> <p>10 THE WITNESS: Not all of</p> <p>11 them. Some substances don't</p> <p>12 induce cell proliferation. They</p> <p>13 act with DNA directly.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You told me earlier there</p> <p>16 was a four-step process to mesothelioma,</p> <p>17 correct, and one of them was cell</p> <p>18 proliferation; is that right?</p> <p>19 A. These are changes that we</p> <p>20 have studied called epigenetic, meaning</p> <p>21 that they don't occur at the level of the</p> <p>22 DNA. And that's been the focus of our</p> <p>23 lab.</p> <p>24 I don't want to give you the</p>

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<p style="text-align: right;">Page 54</p> <p>1 impression that that's the only way that</p> <p>2 mesothelioma develops. That's what we</p> <p>3 focused on.</p> <p>4 Q. All right. Maybe a better</p> <p>5 term is cell proliferation is a</p> <p>6 characteristic of a cancer-causing</p> <p>7 substance. Would you agree with that?</p> <p>8 A. No, I wouldn't.</p> <p>9 As I mentioned, there are a</p> <p>10 lot of agents that don't induce cell</p> <p>11 proliferation that cause cancer.</p> <p>12 Q. Does -- does asbestos induce</p> <p>13 cell proliferation or cause it?</p> <p>14 A. It depends upon the type and</p> <p>15 the dose. Again, we've shown that for</p> <p>16 crocidolite and amosite asbestos in our</p> <p>17 models.</p> <p>18 Q. We don't know why some</p> <p>19 carcinogens are site-specific in the</p> <p>20 human body, correct?</p> <p>21 A. That's a broad statement.</p> <p>22 But yes, we know -- we don't know why</p> <p>23 some agents aren't site specific.</p> <p>24 Q. SNPs or single nucleotide</p>	<p style="text-align: right;">Page 56</p> <p>1 to be one mechanism, whereas some</p> <p>2 hereditary cancers or cancers due to</p> <p>3 agents that focus on the break of DNA</p> <p>4 exert their effects."</p> <p>5 Can I rely on that answer?</p> <p>6 A. Yes.</p> <p>7 MR. FROST: Objection to</p> <p>8 form.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Thank you. You talked about</p> <p>11 ATF3 a minute ago. But ATF3 is a gene,</p> <p>12 and it's also a transcription factor,</p> <p>13 right?</p> <p>14 A. It's a gene, it's a protein,</p> <p>15 and it's a transcription factor.</p> <p>16 Q. And would you agree with me</p> <p>17 that ATF3 is a gene -- the ATF3 gene is</p> <p>18 important in combatting inflammation in</p> <p>19 cells?</p> <p>20 MR. FROST: Objection to</p> <p>21 form.</p> <p>22 THE WITNESS: It depends</p> <p>23 upon the cell and the other</p> <p>24 transcription factors. In our</p>
<p style="text-align: right;">Page 55</p> <p>1 polymorphisms, are mechanisms where some</p> <p>2 cancers due to exposure to agents can</p> <p>3 cause DNA changes that could lead to</p> <p>4 cancer development, correct?</p> <p>5 MR. FROST: Objection to</p> <p>6 form.</p> <p>7 THE WITNESS: Yes, SNPs are</p> <p>8 generally something that occurs in</p> <p>9 a population of cells. It's very</p> <p>10 unusual. In fact, I've never seen</p> <p>11 an agent such as asbestos that</p> <p>12 induces an SNP.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Can you go to your Brower</p> <p>15 deposition, please, ma'am.</p> <p>16 Page 87. If you'll go down</p> <p>17 to Line 13.</p> <p>18 "Question: What are SNPs or</p> <p>19 SNiPs or single nucleotide polymorphisms?</p> <p>20 "Answer: Those are changes</p> <p>21 in DNA.</p> <p>22 "Question: And how do they</p> <p>23 influence the development of cancer?</p> <p>24 "Answer: They are thought</p>	<p style="text-align: right;">Page 57</p> <p>1 experiments, we showed that it</p> <p>2 combatted changes by asbestos;</p> <p>3 that is, it decreased cytokines</p> <p>4 that are associated with</p> <p>5 development of tumors or immune</p> <p>6 response.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. I'm going to ask you, I'm</p> <p>9 going to read a sentence to you and ask</p> <p>10 if you agree with it. "Stress-inducible</p> <p>11 transcription factors play a pivotal role</p> <p>12 in cellular adaptation to environment, to</p> <p>13 maintain homeostasis, and integrity of</p> <p>14 the genome."</p> <p>15 Would you agree with that</p> <p>16 statement?</p> <p>17 MR. FROST: Object to form.</p> <p>18 And I also object to you reading</p> <p>19 her sentences from a document that</p> <p>20 you haven't given her.</p> <p>21 Thank you.</p> <p>22 MR. SMITH: Sure.</p> <p>23 THE WITNESS: Thank you.</p> <p>24</p>

15 (Pages 54 to 57)



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<p style="text-align: right;">Page 58</p> <p>1 BY MR. SMITH: 2 Q. This is attached as 3 Exhibit 4. 4 (Document marked for 5 identification as Exhibit 6 Mossman-4.) 7 BY MR. SMITH: 8 Q. "Systems analysis of ATF3 9 and stress response in cancer reveals 10 opposing effects on pro-apoptotic genes 11 in p53 pathway." 12 Do you have that in front of 13 you, Doctor? 14 A. I do. 15 Q. I've attached it as 16 Exhibit 4. The first sentence in the 17 blue box under abstract. It says, 18 "Stress-inducible transcription factors 19 play a pivotal role in cellular 20 adaptation to environment to maintain 21 homeostasis and integrity in the genome." 22 Would you agree with that? 23 A. Yes. 24 Q. "Activating transcription</p>	<p style="text-align: right;">Page 60</p> <p>1 emphasized previously, it would depend 2 upon the type of cell in terms of the 3 effects on that cell type. 4 Q. Would you agree that ATF3 is 5 activated in response to oxidative stress 6 in a cell? 7 A. I would have to review that 8 literature. I don't see that statement 9 here. 10 Q. I'm asking you just the 11 question. 12 A. ATF3 and oxidative stress, I 13 can't recall specific experiments or cell 14 types that oxidants have been added to, 15 such as hydrogen peroxide or those 16 typical to oxidative stress in studies. 17 Q. IL-8 is a cytokine produced 18 during inflammation by lymphocytes; is 19 that correct? 20 A. It's one of the effects. It 21 also can have opposite effects. 22 Q. You've done a study on EMPs 23 or elongated mineral particles; is that 24 correct?</p>
<p style="text-align: right;">Page 59</p> <p>1 factor 3, or ATF3, is induced by a 2 variety of stress and inflammatory 3 conditions and is overexpressed in many 4 kind of cancer cells." 5 Would you agree with that? 6 MR. FROST: Objection to 7 form. It's overexpressed. 8 MR. SMITH: That's what I 9 said. 10 MR. FROST: You said 11 overexpressed. 12 BY MR. SMITH: 13 Q. Okay. Excuse me. Let me 14 read it again. Second sentence. 15 "Activating transcription factor 3, ATF3, 16 is induced by a variety of stress and 17 inflammatory conditions and is 18 overexpressed in many kinds of cancer 19 cells." 20 Would you agree with that? 21 A. I would agree with the first 22 part of that statement. 23 I have not seen the data on 24 many kinds of cancer cells, and as I</p>	<p style="text-align: right;">Page 61</p> <p>1 A. A study? I have done many 2 studies on elongated mineral particles. 3 Q. I was thinking of your most 4 recent study. But you have done several 5 studies on EMPs, correct? 6 A. Elongated mineral particles 7 including asbestos are -- have been 8 subject of my research for over 40 years. 9 Q. And it can be of any type of 10 mineral with certain dimensions that are 11 fibrous in nature that, when in contact 12 with human cells, can cause adverse 13 changes including epigenetic changes that 14 are pathways that can potentially lead to 15 carcinogenesis; is that correct? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yeah, can we 19 pick that statement apart? 20 BY MR. SMITH: 21 Q. Sure. Let's go to the 22 Brower deposition, Page 85. 23 A. Okay. 24 Q. And I'm going to read over</p>

16 (Pages 58 to 61)

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<p style="text-align: right;">Page 62</p> <p>1 two pages, 85, 86 and 87.  2 "Question: What is an EMP?  3 "An EMP is a very broad term  4 for elongated mineral particles, and it  5 could be referring to anything --  6 regardless of whether anything of certain  7 dimensions that are fibrous in nature.  8 It is a term that has been used most  9 recently by some regulatory agencies, but  10 it is very broad in terms of an umbrella  11 of materials that fit into this category.  12 "Question: And I note in  13 your paper that it says EMPs, and you  14 talk about long EMPs greater than 5  15 micrometers in length; is that correct?  16 "That's a cutoff" --  17 answer, excuse me.  18 "That's a cutoff that's been  19 used in terms of fibers that are thought  20 to be important in regulation. It's a  21 term that is controversial to biologists  22 and chemists.  23 "Question: Is it true that  24 by cell's direct contact with EMP, it</p>	<p style="text-align: right;">Page 64</p> <p>1 do you focus on" -- well, I think we've  2 moved on from EMPs."  3 But can I rely on that  4 testimony regarding EMPs?  5 A. Yes.  6 MR. FROST: And I'm just  7 going to lodge the same objections  8 that were in the transcript.  9 BY MR. SMITH:  10 Q. And can EMPs -- can they  11 cause adverse changes, including  12 epigenetic changes that are pathways that  13 could potentially lead to carcinogenesis?  14 A. Can EMPs? Certain ones  15 certainly can.  16 Q. Different grades of talc and  17 asbestos are different and distinct in  18 shape, size, crystallinity and structure;  19 is that correct?  20 MR. FROST: Objection to  21 form. Vague.  22 BY MR. SMITH:  23 Q. Let's break it out.  24 Different grades of talc are</p>
<p style="text-align: right;">Page 63</p> <p>1 causes the cell to react in certain ways?  2 "Answer: Direct contact by  3 any material can cause certain changes in  4 cells, yes.  5 "Question: And cellular  6 reactions to EMP has occurred, would you  7 agree without the EMP binding to any  8 cellular receptors or penetrating the  9 cell itself, correct?  10 "Answer: Could you just  11 state that again? I'm sorry.  12 "Sure.  13 "I missed the first part."  14 Answer.  15 Question: Sure. The  16 cellular reactions that we just discussed  17 to EMPs, they can occur without the EMP  18 binding to any cellular receptors or  19 penetrating the cell?"  20 And your answer was -- and  21 my question was, "Correct?"  22 And the answer was, "Yes."  23 I said, "Question: Okay,  24 what is the function of proteins and why</p>	<p style="text-align: right;">Page 65</p> <p>1 different and distinct in shape, size,  2 crystallinity and structure, correct?  3 MR. FROST: Objection to  4 form, vague.  5 THE WITNESS: Yeah, when you  6 say grades of talc, I'm a -- I'm a  7 little lost there.  8 BY MR. SMITH:  9 Q. Okay. Cosmetic versus  10 industrial. Pharmaceutical versus  11 industrial versus cosmetic. Those are  12 the grades I'm talking about, my  13 definition of grade.  14 Different grades of talc are  15 different and distinct in size, shape,  16 crystallinity and structure; is that  17 correct?  18 MR. FROST: Objection to  19 form.  20 BY MR. SMITH:  21 Q. Or do you know?  22 A. Yeah, I -- in terms of  23 grades of talc, I would assume that's the  24 case, but I don't study grades of talc.</p>

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<p style="text-align: right;">Page 66</p> <p>1 Q. Different types of asbestos 2 are different and distinct in shape, 3 size, crystallinity and structure, 4 correct? 5 A. That's correct. 6 Q. These characteristics may 7 affect the mineral's reactivity to human 8 cells and carcinogenic potency; is that 9 correct? 10 A. That's correct. 11 Q. The type of asbestos and 12 where it's mined, its shape and size all 13 factor in how it reacts to cells; is that 14 correct? 15 A. Yes. 16 Q. And would the same be of 17 different grades of talc, or do you know? 18 MR. FROST: Objection to 19 form. 20 THE WITNESS: I'd have to 21 study the talc to -- at different 22 grades, and I'm not sure how 23 that's separated out. 24 BY MR. SMITH:</p>	<p style="text-align: right;">Page 68</p> <p>1 good, I'm getting ready to roll to 2 a different section. But I'm good 3 or whatever. Just so long -- 4 THE WITNESS: I'm fine. 5 MR. FROST: I think we can 6 keep going. 7 MR. SMITH: Okay. Okay. 8 All right. Fine. 9 BY MR. SMITH: 10 Q. I want to talk to you about 11 some of your experience, Doctor, as an 12 expert. 13 You said you -- you partly 14 retired since 2014. But you've been 15 testifying in litigation since 2014; is 16 that correct? 17 A. That's correct. 18 Q. And approximately 50 to 19 75 percent of your professional time is 20 spent on litigation since 2014; is that 21 correct? 22 A. That's correct. 23 Q. And would this be the vast 24 majority of your current income since</p>
<p style="text-align: right;">Page 67</p> <p>1 Q. And just so we're clear, 2 you've never studied cosmetic-grade talc; 3 is that right? 4 MR. FROST: Objection. If 5 she -- if she knows. 6 THE WITNESS: I've studied 7 industrial talcs. 8 BY MR. SMITH: 9 Q. So you've never studied 10 cosmetic-grade talc; is that correct? 11 A. I have not studied cosmetic 12 talcs as I know it. 13 Q. Do you understand that 14 cosmetic talc is what's in Baby Powder 15 and Shower to Shower, which are the 16 products at issue in this case? 17 A. Yes, I do. 18 Q. Okay. I want to talk to you 19 about your -- 20 MR. SMITH: Do you want to 21 take a break for a minute, for a 22 second? 23 MR. FROST: Do you want to? 24 MR. SMITH: I mean, I'm</p>	<p style="text-align: right;">Page 69</p> <p>1 2014, and that being as an expert 2 witness? 3 A. Yes, sir. 4 Q. I noticed from your prior 5 testimony that you attached to your 6 report that you've testified 65 times for 7 defendants in talc litigation over the 8 past four years; is that correct? 9 A. That includes depositions 10 and trials in some of the same matters, 11 yes. 12 Q. You were an employee of 13 Biomedical and Environmental Consultants 14 in 1998; is that right? 15 A. 1998? No. 16 Q. Do I have the date wrong? I 17 might have -- I might have written that 18 down wrong. 19 A. That was 30 years ago. 20 Q. What dates were you at 21 Biomedical and Environmental Consultants? 22 A. I worked part-time for them 23 for a little less than two years. 1988 24 to perhaps 1990.</p>

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<p style="text-align: right;">Page 70</p> <p>1 Q. I apologize, I wrote it down</p> <p>2 wrong.</p> <p>3 And you worked there with</p> <p>4 Alfred Wehner, right?</p> <p>5 A. I never worked with</p> <p>6 Dr. Wehner. He was the founder of the</p> <p>7 group as I understand it.</p> <p>8 Q. And you also understand that</p> <p>9 he was also a consultant for Johnson &amp;</p> <p>10 Johnson in talc issues, correct?</p> <p>11 MR. FROST: Objection to</p> <p>12 form.</p> <p>13 THE WITNESS: No.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You don't know that?</p> <p>16 A. I know from reading the</p> <p>17 scientific paper, but I don't know about</p> <p>18 his relationships with Johnson &amp; Johnson.</p> <p>19 Q. He served -- excuse me. You</p> <p>20 served as an expert for the Industrial</p> <p>21 Minerals Association; is that correct?</p> <p>22 A. Served as an expert.</p> <p>23 Q. Expert or consultant for the</p> <p>24 Industrial Minerals Association.</p>	<p style="text-align: right;">Page 72</p> <p>1 correspondence, we've gone back through</p> <p>2 in Brower and Leavitt with</p> <p>3 R.T. Vanderbilt, you weren't</p> <p>4 corresponding with them and consulting</p> <p>5 with R.T. Vanderbilt?</p> <p>6 A. I was not consulting with</p> <p>7 them. I was -- received an assignment</p> <p>8 through Dr. Wehner's group for</p> <p>9 correspondence with these individuals. I</p> <p>10 can't tell you the specific assignment.</p> <p>11 It was with someone named</p> <p>12 John Kelse who was their industrial</p> <p>13 hygienist.</p> <p>14 Q. And he was an employee of</p> <p>15 R.T. Vanderbilt, correct?</p> <p>16 A. He was an employee, yes.</p> <p>17 Q. You served as an expert for</p> <p>18 Cyprus Minerals; is that correct?</p> <p>19 A. I have in litigation.</p> <p>20 Q. And you are currently</p> <p>21 serving as an expert for Johnson &amp;</p> <p>22 Johnson and have in the past; is that</p> <p>23 correct?</p> <p>24 A. I have for a little over a</p>
<p style="text-align: right;">Page 71</p> <p>1 A. I have reviewed proposals</p> <p>2 for them, yes.</p> <p>3 Q. And you've served as an</p> <p>4 expert or consultant for Luzenac; is that</p> <p>5 correct?</p> <p>6 A. Not to my knowledge. As a</p> <p>7 consultant, no, I don't think I've</p> <p>8 consulted Luzenac.</p> <p>9 Q. You weren't corresponding</p> <p>10 with Imerys and Luzenac employees on the</p> <p>11 progress report of the Shukla paper along</p> <p>12 with the IMA?</p> <p>13 A. Yes. I wasn't a consultant</p> <p>14 for them. I was a recipient of a small</p> <p>15 grant from something called EUROTALC that</p> <p>16 may have included Luzenac and other</p> <p>17 companies for a brief period of time in</p> <p>18 about 2005.</p> <p>19 Q. And you've served as an</p> <p>20 expert or consultant for R.T. Vanderbilt,</p> <p>21 right?</p> <p>22 A. No. I never had a formal</p> <p>23 arrangement with R.T. Vanderbilt.</p> <p>24 Q. There's plenty of</p>	<p style="text-align: right;">Page 73</p> <p>1 year now, yes.</p> <p>2 Q. You served as an expert on a</p> <p>3 scientific advisory board for Owens</p> <p>4 Corning in the defense of asbestos</p> <p>5 litigation in the 1980s and 1990s; is</p> <p>6 that correct?</p> <p>7 A. That's incorrect. I</p> <p>8 served -- I went to one meeting there in</p> <p>9 19 -- in the 1980s, and one in the 1990s,</p> <p>10 neither of which concerned Owens Corning</p> <p>11 and litigation.</p> <p>12 Q. Can you go to Page 45 of the</p> <p>13 Brower testimony, please.</p> <p>14 Question, Line 1, on Page</p> <p>15 45.</p> <p>16 "Okay. Well, you've</p> <p>17 consulted with or served as an expert for</p> <p>18 companies that produce or sold</p> <p>19 asbestos-containing products, correct:</p> <p>20 "Answer: Could you be more</p> <p>21 explicit?</p> <p>22 "I need to be more explicit</p> <p>23 than whether you served as an expert or</p> <p>24 consulted with companies that produced</p>

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<p>1 products that contained asbestos? 2 "Answer: The only company 3 that I had a relationship with, and it 4 wasn't a long-standing relationship, was 5 that I agreed to be on the scientific 6 advisory board, I think, once in the 7 1980s and once in the 1990s, with other 8 scientists and review inhouse research by 9 Owens Corning." 10 Is that testimony true? 11 A. Yes. That's what I just 12 stated. 13 Q. Okay. Thank you. 14 You also served as an expert 15 for the tobacco industry in the 1980s; is 16 that correct? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: I had one 20 assignment, approximately 30 years 21 ago, through Dr. Wehners' company. 22 BY MR. SMITH: 23 Q. And since 2014 you have -- 24 was the answer to my question yes?</p>	<p>1 much are you -- what are you billing for 2 your time here today? 3 A. \$550 an hour. 4 Q. Is that the same billing 5 rate that you would have for trial, 6 deposition? Do you differentiate? 7 A. Yes. It would be the same 8 rate. 9 Q. When is the next time that 10 you're scheduled to testify at trial? 11 A. I'm testifying in the Olson 12 trial in New York at the latter part of 13 this week. 14 Q. What about after that? 15 MR. FROST: Objection. 16 THE WITNESS: I don't have 17 any trial dates on my calendar. 18 BY MR. SMITH: 19 Q. Earlier we had talked about, 20 you talked about your work with the 21 tobacco industry. I want to attach as an 22 exhibit, which is Exhibit -- I'll hand 23 you a copy, Doctor. 24 (Document marked for</p>
Page 75	Page 77
<p>1 A. You'll have to state it 2 again, sir. 3 Q. You have served as an expert 4 and consultant for the tobacco industry 5 in the 1980s; is that correct? 6 MR. FROST: Same objection. 7 THE WITNESS: Yeah I had one 8 assignment where I did a 9 literature search for a lawyer 10 representing the tobacco industry. 11 BY MR. SMITH: 12 Q. Since 2014, you have served 13 as an expert on behalf of companies that 14 manufacture and sell talc-based products; 15 is that correct? 16 A. That's correct. 17 Q. And that will continue today 18 and into the foreseeable future; is that 19 correct? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: Yes. 23 BY MR. SMITH: 24 Q. I forgot to ask you. How</p>	<p>1 identification as Exhibit 2 Mossman-5.) 3 BY MR. SMITH: 4 Q. I'll attach this as 5 Exhibit 5. This is a January 12, 1990, 6 letter to Mr. Junius McElveen, Esquire. 7 It looks like it's from you. And it's cc 8 to Alfred Wehner. 9 Are you familiar with this 10 document? 11 A. I am. 12 Q. At the beginning you say, 13 "Dear Mr. McElveen, you requested our 14 meeting last week that Mr. Nims" -- "a 15 brief summary of" -- excuse me. "You 16 requested at our meeting last week with 17 Mr. Nims a brief summary of my literature 18 search to date on cellular and molecular 19 mechanisms of carcinogenesis. 20 "I specifically looked for 21 recent research data to substantiate the 22 premise that cigarette smoking prior to 23 1966 would not be sufficient for lung 24 tumor promotion and progression necessary</p>

20 (Pages 74 to 77)



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<p style="text-align: right;">Page 78</p> <p>1 events in the development of tumors 2 during their relatively long latency 3 period in man." 4 Is that what you were -- was 5 that -- that was the task that you were 6 doing? 7 A. The task that I was doing 8 was to do a search on the molecular 9 biology of lung cancers. 10 Q. And the statement that I 11 just read, is that correct? Is that what 12 your task was? Is that what you were 13 doing? 14 A. I'm not sure what cigarette 15 smoking prior to 1966 was relevant to, 16 but I think the question he was asking me 17 were, do components of cigarette smoke 18 have properties that start or influence 19 the development of cancers. 20 Q. And -- but this is your -- 21 you wrote this letter, correct? 22 A. I did. 23 Q. Okay. And on the last 24 paragraph of the letter, before your</p>	<p style="text-align: right;">Page 80</p> <p>1 Owens Corning Fiberglass Corporation, 2 Granville technical center, Granville, 3 Ohio. 4 And it says, "Dear John." 5 And you understand, as you reference in 6 this, that -- that Owens Corning was 7 producing asbestos-containing materials; 8 is that correct? 9 A. No, not at this time point. 10 I was never aware of this in the 1980s. 11 Q. So when you write in the 12 paragraph, final paragraph, "Please find 13 enclosed a brief critique of the recent 14 PNAS covered in the New York Times. I 15 cannot help but surmise that Dr. Selikoff 16 was responsible for the press release. 17 Regardless, the possibility that asbestos 18 binds and introduces malignant and 19 foreign DNA into normal cells of the lung 20 seems highly unlikely." 21 You didn't understand that 22 the issue of asbestos and Owens Corning 23 was relevant to the company? 24 A. No. Dr. Hadley was a</p>
<p style="text-align: right;">Page 79</p> <p>1 signature, it says, "I will continue to 2 survey new journals in the field as well 3 as Index Medica searches on 'genes and 4 lung cancer.' Please let me know when 5 you would like to meet again for an 6 update." 7 And then did you continue to 8 do what you said you would do? 9 A. No. I wrote a final report 10 after meeting these individuals and no 11 longer was a consultant for Biomedical 12 and Environmental Consulting. 13 Q. I'm going to attach what is 14 Exhibit 6 to the deposition another 15 letter from you. And we talked about 16 Owens Corning just a minute ago. Do you 17 recall that, Doctor? 18 A. Yes. 19 (Document marked for 20 identification as Exhibit 21 Mossman-6.) 22 BY MR. SMITH: 23 Q. And here is a letter from 24 you to Owens Corning. Dr. John Hadley,</p>	<p style="text-align: right;">Page 81</p> <p>1 colleague that I met at a scientific 2 meeting. He was responsible for the 3 development of fiberglasses at their 4 technical center. 5 He was also a scientist who 6 attended meetings on asbestos and was 7 interested in the effects of asbestos on 8 cells -- 9 Q. Did you come -- 10 A. -- by training. 11 Q. I'm sorry. I didn't mean to 12 cut you off. 13 A. I'm sorry. By training, 14 John was someone I actually met when he 15 was getting his degree earlier at Duke 16 University. 17 Q. Did you come to learn that 18 as -- Owens Corning produced 19 asbestos-containing products? 20 A. I came to learn that after I 21 heard about their bankruptcy. I was 22 never aware of that directly. 23 Q. You were a member of the 24 TASSC, weren't you?</p>

21 (Pages 78 to 81)

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<p style="text-align: right;">Page 82</p> <p>1 A. TASSC?</p> <p>2 Q. Mm-hmm.</p> <p>3 A. I don't know what that is,</p> <p>4 and I don't think I've ever paid</p> <p>5 membership dues or I would remember.</p> <p>6 MR. SMITH: Can you hand</p> <p>7 that to the witness.</p> <p>8 (Document marked for</p> <p>9 identification as Exhibit</p> <p>10 Mossman-7.)</p> <p>11 BY MR. SMITH:</p> <p>12 Q. I'm going to attach a</p> <p>13 partial listing of key scientists and --</p> <p>14 I don't know if I can pronounce this --</p> <p>15 academicians supporting the advancement</p> <p>16 of sound science coalition. You don't</p> <p>17 recall this? TASSC?</p> <p>18 A. No, I don't think -- I'm</p> <p>19 just looking at some of the people here,</p> <p>20 who are -- include scientists from</p> <p>21 different spheres including Bruce Ames.</p> <p>22 So no, I am not aware that this is a</p> <p>23 society that I ever joined, no.</p> <p>24 Q. So if you go -- and it's in</p>	<p style="text-align: right;">Page 84</p> <p>1 this is an article entitled,</p> <p>2 "Constructing 'Sound Science' and 'Good</p> <p>3 Epidemiology': Tobacco, Lawyers and</p> <p>4 Public" -- "and the Public Relations</p> <p>5 Firms."</p> <p>6 And it's an article in the</p> <p>7 American Journal of Public Health from</p> <p>8 November of 2001. It's a peer-reviewed</p> <p>9 article. And it's by lead author Ong.</p> <p>10 And it goes down, and if you</p> <p>11 look on the front page, Doctor, it says,</p> <p>12 "Philip Morris' 'Sound Science'</p> <p>13 organization in the United States"?</p> <p>14 Says, "PM," Philip Morris,</p> <p>15 "began its 'sound science' program in</p> <p>16 1993 to stimulate criticism of the 1992</p> <p>17 U.S. Environmental Protection Agency</p> <p>18 (EPA) report, which identified secondhand</p> <p>19 smoke as a Group A human carcinogen.</p> <p>20 Ellen Merlo (vice president, PM Corporate</p> <p>21 Affairs) wrote to William Campbell</p> <p>22 (chairman at PM" -- or Philip Morris --</p> <p>23 "USA)."</p> <p>24 Then it goes on to the -- go</p>
<p style="text-align: right;">Page 83</p> <p>1 alphabetical order. And on Page 9,</p> <p>2 looking at the top, there's your name.</p> <p>3 Dr. Brooke T. Mossman, professor of</p> <p>4 pathology, College of Medicine,</p> <p>5 University of Vermont, Burlington,</p> <p>6 Vermont. Is that you?</p> <p>7 A. That's me.</p> <p>8 Q. And you are listed on the</p> <p>9 partial listing of key scientists and</p> <p>10 academicians -- butchering that name --</p> <p>11 supporting the advancement of sound</p> <p>12 science coalition, TASSC. Do you see</p> <p>13 that, Doctor?</p> <p>14 A. Yes, I have no idea what</p> <p>15 that is. Sorry.</p> <p>16 Q. Well, maybe we can put some</p> <p>17 context to it here today.</p> <p>18 MR. SMITH: Thank you.</p> <p>19 (Document marked for</p> <p>20 identification as Exhibit</p> <p>21 Mossman-8.)</p> <p>22 BY MR. SMITH:</p> <p>23 Q. I'm going to attach the next</p> <p>24 numbered exhibit which is Number 8. And</p>	<p style="text-align: right;">Page 85</p> <p>1 to the right paragraph, "In February of</p> <p>2 1993, Philip Morris, PM, and its public</p> <p>3 relations firm, APCO Associates, worked</p> <p>4 to launch a 'sound science' coalition in</p> <p>5 the United States with approximately</p> <p>6 320,000 budgeted for the first 24 weeks.</p> <p>7 Three months later, The Advancement For</p> <p>8 Sound Science Coalition, or TASSC, has</p> <p>9 been formed. TASSC described itself as a</p> <p>10 'a not-for-profit coalition advocating</p> <p>11 the use of sound science in public policy</p> <p>12 decisionmaking' even though APCO created</p> <p>13 it to help Philip Morris fight smoking</p> <p>14 restrictions. TASSC's public positioning</p> <p>15 and media campaign were designed to</p> <p>16 minimize its connections with the tobacco</p> <p>17 industry. TASSC's member survey</p> <p>18 mentioned only secondhand smoke among a</p> <p>19 list of other potential examples of</p> <p>20 'unsound, incomplete or unsubstantiated</p> <p>21 science.'"</p> <p>22</p> <p>23 Were you familiar with all</p> <p>24 of this, Doctor, and have you seen this</p>

22 (Pages 82 to 85)

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<p style="text-align: right;">Page 86</p> <p>1 article before?</p> <p>2 A. I haven't seen the article,</p> <p>3 but let me emphasize that I've never been</p> <p>4 a member by consent of TASSC, and there's</p> <p>5 no reason that tobacco would have wanted</p> <p>6 me to be a member, as all my publications</p> <p>7 list tobacco smoke as the Number 1 cause</p> <p>8 of lung disease or lung cancers.</p> <p>9 Q. Well, you -- you haven't</p> <p>10 published any articles on secondhand</p> <p>11 smoke, have you?</p> <p>12 MR. FROST: Objection, form.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Have you?</p> <p>15 A. Secondhand smoke, no.</p> <p>16 Q. Okay. You mentioned all of</p> <p>17 your research as best -- you mentioned</p> <p>18 all of your research on asbestos, talc</p> <p>19 and cleavage fragments have been</p> <p>20 published and peer-reviewed, high-impact</p> <p>21 scientific journals prior to the event --</p> <p>22 advent of your participation in talc</p> <p>23 litigation in 2014. And that's listed in</p> <p>24 your report.</p>	<p style="text-align: right;">Page 88</p> <p>1 A. When you say -- when you say</p> <p>2 it would --</p> <p>3 Q. Your research being</p> <p>4 published in peer-reviewed high-impact</p> <p>5 scientific journals on asbestos, asbestos</p> <p>6 fibers, talc and cleavage fragments.</p> <p>7 A. Let me emphasize that I'm</p> <p>8 not doing original research anymore on</p> <p>9 talc or asbestos fibers. So that</p> <p>10 statement would not be relevant.</p> <p>11 Q. Okay. Fair enough. I want</p> <p>12 to look at your CV for a second.</p> <p>13 A. Okay.</p> <p>14 Q. And I've got an extra copy</p> <p>15 for you. Several actually.</p> <p>16 MR. FROST: Is this the CV</p> <p>17 that was attached to the report?</p> <p>18 MR. SMITH: It is.</p> <p>19 (Document marked for</p> <p>20 identification as Exhibit</p> <p>21 Mossman-9.)</p> <p>22 BY MR. SMITH:</p> <p>23 Q. All right. Now, you've</p> <p>24 got -- do you have your CV in front of</p>
<p style="text-align: right;">Page 87</p> <p>1 Do you recall saying that?</p> <p>2 A. Yes.</p> <p>3 Q. I'll assume that would mean</p> <p>4 that that would be the same after your</p> <p>5 involvement in talc litigation. Would</p> <p>6 that be correct?</p> <p>7 A. I'm not sure what you're</p> <p>8 asking.</p> <p>9 Q. Let me rephrase. Let me</p> <p>10 rephrase it.</p> <p>11 A. Okay.</p> <p>12 Q. That was confusing.</p> <p>13 You -- in your report you</p> <p>14 mentioned that your research on asbestos</p> <p>15 fibers, talc, and cleavage fragments have</p> <p>16 been published and peer-reviewed</p> <p>17 high-impact scientific journals prior to</p> <p>18 the advent of your participation in talc</p> <p>19 litigation in 2014?</p> <p>20 A. Yes.</p> <p>21 Q. You agreed with that.</p> <p>22 And I would assume that</p> <p>23 would be the same after your involvement</p> <p>24 post 2014; is that correct?</p>	<p style="text-align: right;">Page 89</p> <p>1 you, Doctor?</p> <p>2 A. I do.</p> <p>3 Q. Okay. And I would like to</p> <p>4 go to Page 15.</p> <p>5 MR. SMITH: I'm going to</p> <p>6 attach this as the next numbered</p> <p>7 exhibit. It's Number 9.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. It says -- it should be</p> <p>10 referred. It says refereed. Is that --</p> <p>11 should it be referred manuscripts?</p> <p>12 A. No.</p> <p>13 Q. Is that -- am I missing</p> <p>14 something?</p> <p>15 A. No, it's refereed.</p> <p>16 Q. Well, then I -- I'm learning</p> <p>17 something new everyday.</p> <p>18 Manuscripts, book chapters,</p> <p>19 monographs and editorials, in parentheses</p> <p>20 peer reviewed.</p> <p>21 A. Correct.</p> <p>22 Q. Hold on. I'm getting ahead</p> <p>23 of myself.</p> <p>24 Let's go back to Page 2.</p>

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<p style="text-align: right;">Page 90</p> <p>1 A. Okay.</p> <p>2 Q. And you have reviewer and in</p> <p>3 parentheses journals. And this is all of</p> <p>4 the journals that you have served as a</p> <p>5 reviewer of?</p> <p>6 A. Yes.</p> <p>7 Q. And then if we go to Page 3,</p> <p>8 and you look at that section, it's the</p> <p>9 fourth from the bottom, Regulatory</p> <p>10 Pharmacology and Toxicology. You served</p> <p>11 as a reviewer for that publication; is</p> <p>12 that correct, according to your CV?</p> <p>13 A. Let's see. Could you go to</p> <p>14 the page again?</p> <p>15 Q. Sure. It's Page 3. And if</p> <p>16 you go up, it's under -- like at the top,</p> <p>17 it's got the list of journals, and if you</p> <p>18 see science at the bottom, then you see</p> <p>19 scanning electron microscopy, and then --</p> <p>20 A. Yes.</p> <p>21 Q. -- you see risk analysis,</p> <p>22 then you see Regulatory Pharmacology and</p> <p>23 Toxicology.</p> <p>24 Do you see that?</p>	<p style="text-align: right;">Page 92</p> <p>1 (Document marked for</p> <p>2 identification as Exhibit</p> <p>3 Mossman-10.)</p> <p>4 BY MR. SMITH:</p> <p>5 Q. Okay. And you see it's</p> <p>6 written by David Michaels. And if you go</p> <p>7 to the very last page. It says, "David</p> <p>8 Michaels is an epidemiologist and the</p> <p>9 director of the project on scientific</p> <p>10 knowledge and public policy at the George</p> <p>11 Washington University School of Public</p> <p>12 Health and Health Services.</p> <p>13 "During the Clinton</p> <p>14 administration he served as assistant</p> <p>15 secretary of energy for environment,</p> <p>16 safety and health responsible for</p> <p>17 protecting the health and safety of</p> <p>18 workers, neighboring communities, and the</p> <p>19 environment surrounding the nation's</p> <p>20 nuclear weapons facilities. He was the</p> <p>21 architect of the historic initiative that</p> <p>22 'made peace with the past,' compensating</p> <p>23 U.S. nuclear weapons workers for</p> <p>24 illnesses developed while making or</p>
<p style="text-align: right;">Page 91</p> <p>1 A. Yes, I reviewed for them.</p> <p>2 Q. Okay. And I want to talk</p> <p>3 about the Journal of Regulatory</p> <p>4 Toxicology and Pharmacology for a second.</p> <p>5 Do you believe this is a</p> <p>6 reputable independent journal?</p> <p>7 A. Yes, I believe it is.</p> <p>8 Historically I've heard a lot about it.</p> <p>9 Q. Do you know who David</p> <p>10 Michaels is?</p> <p>11 A. No.</p> <p>12 Q. You served as a peer</p> <p>13 reviewer of him on the NIOSH 62 bulletin.</p> <p>14 You don't know him, that used to work in</p> <p>15 the federal government?</p> <p>16 A. I -- no, the name doesn't</p> <p>17 ring a bell.</p> <p>18 Q. Well, he wrote a book called</p> <p>19 "Doubt is Their Product: How Industry's</p> <p>20 Assault on Science Threatens Your</p> <p>21 Health."</p> <p>22 And I'd like -- do you have</p> <p>23 a copy in front of you, Doctor?</p> <p>24 A. I do.</p>	<p style="text-align: right;">Page 93</p> <p>1 testing atomic weapons.</p> <p>2 "In 2006 Michaels received</p> <p>3 an American Association" -- "received the</p> <p>4 American Association For the Advancement</p> <p>5 of Science" -- "Sciences, Scientific</p> <p>6 Freedom and Responsibility Award. He</p> <p>7 lives in Bethesda, Maryland."</p> <p>8 And that doesn't ring any</p> <p>9 bells?</p> <p>10 A. No, I don't recognize him</p> <p>11 and I don't recognize the name.</p> <p>12 Q. If you'll go to -- it's on</p> <p>13 Page -- it's the fourth or fifth page in.</p> <p>14 If you look at the top, it's Page 53.</p> <p>15 And he discusses this</p> <p>16 publication for which he served as a</p> <p>17 reviewer on.</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Quote down at the bottom,</p> <p>21 "There is now a slew of these captured</p> <p>22 journals. The tobacco industry, for</p> <p>23 example, secretly financed the journal</p> <p>24 Indoor and Billet Environment to promote</p>

24 (Pages 90 to 93)

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<p style="text-align: right;">Page 94</p> <p>1 and position for legal purposes the idea 2 that indoor air pollution was a problem 3 caused not by secondhand smoke but by 4 inadequate ventilation. The best known 5 of these publications is Regulatory 6 Toxicology and Pharmacology, the official 7 mouthpiece of the International Society 8 of Regulatory Toxicology and Pharmacology 9 or ISRTP, an impressive name, but really 10 just an association dominated by 11 scientists who work for industry trade 12 groups and consulting firms. 13 "The sponsor of the ISRTP 14 include many of the major tobacco, 15 chemical, and drug manufacturing 16 companies. Its leadership consists of 17 corporate and product defense scientists 18 and attorneys along with a small number 19 of government scientists who have 20 apparently bought in or who do not know 21 better. 22 "The immediate past 23 president was Terry Quill, an attorney 24 who became a senior vice president for</p>	<p style="text-align: right;">Page 96</p> <p>1 academic scientists and I'm not 2 sure of the context of this or the 3 years that this covers. 4 Again, I've reviewed for 5 them in the past. I have not been 6 on their editorial board, so I 7 really can't comment on this. 8 BY MR. SMITH: 9 Q. Do you know what the 10 Weinberg Group's involvement has been in 11 talc litigation or defense of talc? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: No. 15 BY MR. SMITH: 16 Q. I'd like to show you another 17 article. 18 (Document marked for 19 identification as Exhibit 20 Mossman-11.) 21 BY MR. SMITH: 22 Q. Attached as the next 23 numbered exhibit. Attached -- Doubt is 24 Their Product was Exhibit 10. This is</p>
<p style="text-align: right;">Page 95</p> <p>1 the product defense of" -- excuse me -- 2 "product defense of the Weinberg Group. 3 Quill also has roots in the tobacco wars, 4 but is not a scientific expert. Rather 5 he served as outside counsel to Philip 6 Morris in the secondhand smoke 7 litigation." 8 Have you ever seen that 9 written about Regulatory Toxicology and 10 Pharmacology, the journal that you served 11 as a reviewer of? 12 MR. FROST: I'll say -- 13 first, I'll just object to using 14 what is basically an opinion piece 15 in this case. 16 But you can answer the 17 question, Brooke. 18 THE WITNESS: Yeah, I'm not 19 familiar with what this source is. 20 It looks like a book chapter. 21 Again, Regulatory Toxicology and 22 Pharmacology is -- historically 23 has been a journal that has been 24 well regarded by government and</p>	<p style="text-align: right;">Page 97</p> <p>1 going to be Exhibit 11. 2 This is an article entitled 3 "Special Contributions: Correspondence 4 About Public Ethics and Regulatory 5 Toxicology and Pharmacology." 6 This is -- this is published 7 in a peer-reviewed journal called the 8 International Journal of Occupational and 9 Environmental Health. And it was in 10 November 19, 2002. And I'm going to read 11 from the -- from the top. 12 MR. FROST: Okay. I just 13 want to object to any connotation 14 that this letter is peer-reviewed. 15 BY MR. SMITH: 16 Q. "In this issue, IJOEH is 17 publishing correspondence concerning 18 conflicts of interest, lack of 19 transparency and absence of editorial 20 independence of the journal Regulatory 21 Toxicology and Pharmacology, RTP." 22 That's where you served as a 23 peer reviewer, right? 24 A. I was asked once or twice to</p>



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<p style="text-align: right;">Page 98</p> <p>1 review articles for them. I have no idea 2 when this was. And I have no idea who 3 forwarded me the papers for review. 4 Q. Ma'am, I'm just reading from 5 your CV, and you said that you were a 6 reviewer of Regulatory Toxicology and 7 Pharmacology, correct? 8 A. I have reviewed papers for 9 that journal. 10 Q. "Regulatory Toxicology and 11 Pharmacology is the official publication 12 of the industry-funded International 13 Society of Regulatory Toxicology and 14 Pharmacology or IS RTP." Then it goes 15 down into the second -- third paragraph. 16 "IJOEH has chosen to publish this 17 exchange in order to alert readers to the 18 ways in which supposedly credible 19 peer-reviewed journals may be co-opted by 20 corporations seeking to give credibility 21 to particular scientific points of view. 22 "RTP publishes a large 23 number of studies conducted by 24 industry-funded scientists. These</p>	<p style="text-align: right;">Page 100</p> <p>1 Excuse me, ma'am. 2 THE WITNESS: Pardon me? 3 MS. O'DELL: "Object to the 4 form" is the appropriate 5 objection. 6 MR. FROST: I'll try to 7 remember that. 8 BY MR. SMITH: 9 Q. And then I want to go on 10 further. It says, "November 19, 2002, 11 Ms. Kirsten Chrisman, managing editor, 12 Journals Division, Academic Press. And a 13 Paul Weislogel, vice president, global 14 Society, of Elsevier, Science, Inc. Are 15 you familiar with that publication? 16 They publish a lot of 17 scientific literature. 18 A. Who is this now? 19 Q. I might be pronouncing the 20 name -- Elsevier Science, Inc.? 21 A. Yes. I'm looking at the 22 journal, though, sir. And this is a 23 letter, and it's signed by a number of 24 individuals, several whom I recognize as</p>
<p style="text-align: right;">Page 99</p> <p>1 studies later become part of industry's 2 efforts to influence federal regulatory 3 agencies or defend litigation claims 4 concerning toxic exposure. 5 "Without safeguards to 6 assure their independence of the 7 editorial process, suspicion, some of it 8 well deserved, is cast over studies and 9 journals." 10 And that was written by the 11 editor-in-chief of this publication. 12 Do you see that? 13 MR. FROST: Again, I object 14 to the use of what is clearly an 15 opinion piece to try to establish 16 facts in this case and in 17 questioning this witness. 18 THE WITNESS: If I can -- 19 MS. O'DELL: "Object to the 20 form" -- 21 THE WITNESS: If I can look 22 at the -- 23 MS. O'DELL: -- is the 24 appropriate objection.</p>	<p style="text-align: right;">Page 101</p> <p>1 plaintiff experts. 2 Q. Ma'am, there's not a 3 question on the table. I'm going to ask 4 you a question though. Okay. 5 MR. FROST: Well, I think 6 you did ask a question. 7 THE WITNESS: Well, I think 8 you asked me to look at this, and 9 I would give this, based upon the 10 signatures here, that this is not 11 a peer-reviewed letter. And that 12 it's not relevant. It looks like 13 a letter that was written. It 14 certainly was not peer-reviewed 15 and again, I want to emphasize 16 that this publication that you're 17 questioning is the official 18 publication of a society of which 19 I am not a member. 20 BY MR. SMITH: 21 Q. Ma'am, do we need to go back 22 to your CV again where you were listed as 23 a peer reviewer of this publication? 24 A. I did not review this</p>

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<p style="text-align: right;">Page 102</p> <p>1 publication.</p> <p>2 Q. You're not a -- you're not a</p> <p>3 peer reviewer of Regulatory Toxicology</p> <p>4 and Pharmacology?</p> <p>5 A. I, in the past, through</p> <p>6 perhaps 40 years, have reviewed papers</p> <p>7 for them.</p> <p>8 Q. And that's the extent --</p> <p>9 A. It could have been one or --</p> <p>10 Q. That's your extent of</p> <p>11 involvement with Regulatory Toxicology</p> <p>12 and Pharmacology?</p> <p>13 A. I have never been on their</p> <p>14 editorial board, and I know little about</p> <p>15 the journal. I'm not a member of the</p> <p>16 society of -- that disseminates this</p> <p>17 journal.</p> <p>18 Q. I'm going to read the</p> <p>19 document, "Dear Ms. Chrisman and Mr.</p> <p>20 Weislogel, we write you to express our</p> <p>21 concerns about apparent conflicts of</p> <p>22 interest, lack of transparency, and the</p> <p>23 absence of editorial independence of the</p> <p>24 Journal of Regulatory Toxicology and</p>	<p style="text-align: right;">Page 104</p> <p>1 trade association that have direct</p> <p>2 incentive to minimize the regulatory</p> <p>3 burden on industry, Bullet Point 2.</p> <p>4 "A significant percentage of</p> <p>5 members of the RTP editorial board have</p> <p>6 financial ties to companies whose</p> <p>7 products or byproducts are the subject of</p> <p>8 studies published by the RTP."</p> <p>9 Next, down at the bottom of</p> <p>10 Page 387, "RTP editorial's commonly</p> <p>11 support industry, antiregulatory goals."</p> <p>12 Next bullet point: "RTP</p> <p>13 serves as a convenient venue for</p> <p>14 publication of industry research and</p> <p>15 gives the credibility of a peer-reviewed</p> <p>16 journal to articles that may not have</p> <p>17 been subjected to full and meaningful</p> <p>18 independent review."</p> <p>19 Next bullet point: "RTP</p> <p>20 routinely fails to disclose relevant</p> <p>21 conflicts of interest."</p> <p>22 Then it goes on to the next</p> <p>23 section. "Given the considerable</p> <p>24 industry support received by ISRTP, RTP's</p>
<p style="text-align: right;">Page 103</p> <p>1 Pharmacology, RTP, which you publish.</p> <p>2 "As you know, that journal</p> <p>3 is the official publication of the</p> <p>4 International Society of Regulatory</p> <p>5 Toxicology and Pharmacology or ISRTP.</p> <p>6 Our concerns about Regulatory Toxicology</p> <p>7 and Pharmacology include:"</p> <p>8 Bullet point, "The journal's</p> <p>9 apparent bias in favor of industries that</p> <p>10 are subject to governmental health and</p> <p>11 environmental regulations that provide</p> <p>12 financial support to RTP's sponsor,</p> <p>13 ISRTP.</p> <p>14 "ISRTP is supported by,</p> <p>15 among others, the American Chemical</p> <p>16 Council" -- "Chemistry Council,</p> <p>17 Bristol-Myers Squibb Company, Dow</p> <p>18 AgroSciences, Eastman Kodak, Gillette</p> <p>19 Company, In-Spec Chemical Corporation.</p> <p>20 Merck &amp; Co., Inc., Procter &amp; Gamble,</p> <p>21 R.J. Reynolds Tobacco Company, The</p> <p>22 Sapphire Group, Inc., Schering-Plough</p> <p>23 Research Institute, and SmithKline</p> <p>24 Beecham Pharmaceuticals, all companies or</p>	<p style="text-align: right;">Page 105</p> <p>1 industry oriented editorial board, the</p> <p>2 too-frequent antiregulatory tenor of</p> <p>3 RTP's editorials, and the preponderance</p> <p>4 of publications by industry-funded</p> <p>5 scientists, we urge Academic</p> <p>6 Press/Elsevier to" -- I'm mispronouncing</p> <p>7 that name -- "to increase the credibility</p> <p>8 of the journal by insisting that RTP, (1)</p> <p>9 sever its ties to the industry-sponsored</p> <p>10 ISRTP; (2) reconstitute its advisory</p> <p>11 board to dramatically reduce the</p> <p>12 influence of industry scientists,</p> <p>13 industry lawyers, and academic</p> <p>14 consultants to industry; and (3) adopt an</p> <p>15 editorial policy about conflicts of</p> <p>16 interest."</p> <p>17 And then at the end of</p> <p>18 the -- of this letter in this</p> <p>19 peer-reviewed journal, it has signed by</p> <p>20 one -- let's see. One, two, three, four</p> <p>21 -- 32, excuse me, that's another page.</p> <p>22 It goes onto the next page.</p> <p>23 42 different Ph.D.s,</p> <p>24 doctors, of all walks through the United</p>

27 (Pages 102 to 105)

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<p>1 States and around the world, from 2 different institutions, different 3 hospitals -- do you see that, Doctor? 4 MR. FROST: I'm going to 5 object. Wonderful testimony you 6 just gave. 7 Again I'm going to object to 8 the use of an opinion piece. I'll 9 object to just reading from 10 something that, first off is -- 11 MR. SMITH: Just state your 12 objection. I don't need a 13 speaking objection. 14 MR. FROST: -- second -- 15 MR. SMITH: I don't need a 16 speaking objection. 17 MR. FROST: But I think this 18 entire line of questioning, quite 19 frankly, is completely improper. 20 And as Dr. Mossman said, 21 she's never seen this before. And 22 we've already established that 23 this is just an opinion piece 24 that's signed on by several</p>	<p>1 do we have a Special Master in 2 this case? 3 MS. O'DELL: Yes. 4 MR. SMITH: All right. So 5 I've warned you, I've done it 6 twice now. I mean -- okay. All 7 right. 8 BY MR. SMITH: 9 Q. Have you seen this piece, 10 Doctor? 11 A. I have not. And I'm not a 12 member of the editorial board of this 13 journal. And these individuals, as I 14 point out, are people who -- many of whom 15 are involved as plaintiff expert 16 witnesses in litigation. And that I do 17 recognize. 18 Q. Okay. 19 A. I would also -- 20 Q. I know you said -- I'm 21 sorry? 22 A. I -- I also want to bring up 23 the point that International Journal of 24 Occupational and Environmental Health,</p>
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<p>1 plaintiffs' attorneys. Answer 2 your question -- 3 MR. SMITH: Look, I'm going 4 to let -- I'm going to let you go. 5 There are no more speaking 6 objections; otherwise, I'm going 7 to get the Court on the phone. 8 You can speak -- you can voice 9 your objection, but we're not 10 going to have speaking objections. 11 MR. FROST: Well, we'll see. 12 I mean, I've -- as I've said, I 13 just -- I'm objecting to the 14 proprietary of even using, you 15 know, this example. 16 Just sitting there and 17 reading a -- a letter into the 18 record and not asking a question 19 about it, is not the proper -- 20 MR. SMITH: I'll get the 21 Court involved. If you're going 22 to continue to speak, do speaking 23 objections, I'm going to call -- 24 I -- we have a Special Master --</p>	<p>1 I'm not sure that journal still exists. 2 If this is the one, as the letter is 3 signed, that Dr. Egilman was editor of 4 this journal, has been dropped by 5 Elsevier. 6 Q. Well, let's talk about a 7 few -- a few studies. Did you publish a 8 publication called "Assessment of the 9 pathogenic potential of asbestiform 10 versus non-asbestiform particulates 11 (cleavage fragments) in in vitro (cell or 12 organ culture) models and bioassays"? 13 A. Yes. I -- that was the 14 paper that I published in this journal. 15 Q. And, in fact, it was 16 published in the Regulatory Toxicology 17 and Pharmacology publication that we just 18 went over all this? 19 MR. FROST: Form. 20 THE WITNESS: I just said 21 that. 22 BY MR. SMITH: 23 Q. You just told me earlier 24 that your only involvement with this</p>

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<p style="text-align: right;">Page 110</p> <p>1 publication was looking at two</p> <p>2 peer-reviewed articles. You didn't state</p> <p>3 anything about actually publishing on the</p> <p>4 assessment of the pathogenic potential of</p> <p>5 asbestiform versus cleavage fragments.</p> <p>6 You didn't state that earlier when you --</p> <p>7 when you talked about your review --</p> <p>8 A. Sir --</p> <p>9 Q. -- your time -- excuse me.</p> <p>10 As your time as a reviewer for this</p> <p>11 publication, did you?</p> <p>12 MR. FROST: Objection to</p> <p>13 form.</p> <p>14 THE WITNESS: You -- you did</p> <p>15 not ask me if I published in this</p> <p>16 journal.</p> <p>17 Yes, I have an article</p> <p>18 published in this journal.</p> <p>19 (Document marked for</p> <p>20 identification as Exhibit</p> <p>21 Mossman-12.)</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Well, ma'am, you told me,</p> <p>24 and I can have them read it back to you,</p>	<p style="text-align: right;">Page 112</p> <p>1 Q. Well, let's -- let's look at</p> <p>2 it. Your conclusions of assessing</p> <p>3 whether -- of the pathogenic potential of</p> <p>4 asbestos versus non-asbestiform cleavage</p> <p>5 fragments. We look at the abstract, and</p> <p>6 in the last sentence, "The available</p> <p>7 studies show that cleavage fragments are</p> <p>8 less bioreactive and cytotoxic than</p> <p>9 asbestiform fibers."</p> <p>10 Was that your conclusion?</p> <p>11 A. That is the conclusion based</p> <p>12 upon all my peer-reviewed papers that</p> <p>13 have been published on this topic. Yes.</p> <p>14 This is a review.</p> <p>15 MR. SMITH: I'll attach that</p> <p>16 as Exhibit 12.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. And on your reference</p> <p>19 materials that you have for this case</p> <p>20 that I received, you have an article by</p> <p>21 Alfred Wehner. "Cosmetic Talc Should Not</p> <p>22 Be Listed As a Carcinogen: Comments on</p> <p>23 NTP Deliberations to Talc As a</p> <p>24 Carcinogen."</p>
<p style="text-align: right;">Page 111</p> <p>1 that the only involvement you had with</p> <p>2 this publication was reviewing two</p> <p>3 articles. Do we need to go back to the</p> <p>4 testimony?</p> <p>5 MR. FROST: Objection to</p> <p>6 form.</p> <p>7 THE WITNESS: I'm sorry,</p> <p>8 sir, but you were asking me about</p> <p>9 Page 3 on my CV, which lists</p> <p>10 journals that I have reviewed for.</p> <p>11 And the questions that you</p> <p>12 asked me I answered with regard to</p> <p>13 my editorial responsibility in</p> <p>14 reviewing a paper or two for this</p> <p>15 journal.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. You left out that you</p> <p>18 actually published in the journal too?</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: I -- I</p> <p>22 acknowledge that I published in</p> <p>23 the journal.</p> <p>24 BY MR. SMITH:</p>	<p style="text-align: right;">Page 113</p> <p>1 Do you recall that?</p> <p>2 A. I do.</p> <p>3 Q. You also listed a paper by</p> <p>4 Mr. Zazenski, who -- it's entitled "Talc:</p> <p>5 Occurrence, Characterization and Consumer</p> <p>6 Applications."</p> <p>7 Do you see that? Do you</p> <p>8 recall that?</p> <p>9 A. Yes.</p> <p>10 Q. Okay. Did you know both of</p> <p>11 those were published in Regulatory</p> <p>12 Toxicology and Pharmacology?</p> <p>13 A. I don't recall that. But --</p> <p>14 Q. Let's look at them.</p> <p>15 MR. FROST: Which one? Are</p> <p>16 you going to mark this?</p> <p>17 MR. SMITH: I'm going to</p> <p>18 mark Alfred Wehner's publication</p> <p>19 as Exhibit 13. And Zazenski as</p> <p>20 14.</p> <p>21 (Document marked for</p> <p>22 identification as Exhibit</p> <p>23 Mossman-13.)</p> <p>24 (Document marked for</p>

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<p style="text-align: right;">Page 114</p> <p>1 identification as Exhibit 2 Mossman-14.) 3 BY MR. SMITH: 4 Q. And let's look at both of 5 these. So, we have -- we went over 6 Regulatory Toxicology and Pharmacology, 7 what David Michaels wrote about them, 8 what was in the International Journal of 9 Occupational and Environmental Health 10 that you had not seen before. We went 11 over your publication in that journal, 12 which we just talked about and discussed 13 your opinion in the abstract that when 14 looking at asbestos versus the cleavage 15 fragments, you concluded the available 16 studies showed that cleavage fragments 17 are less bioreactive and cytotoxic than 18 asbestiform fibers. 19 Now we'll move to 20 Dr. Wehner's assessment in the same 21 journal. And if you look down at his 22 conclusion in the abstract, "Considering 23 talc as a carcinogen lacks convincing 24 scientific documentation."</p>	<p style="text-align: right;">Page 116</p> <p>1 consumers." And then he quotes Alfred 2 Wehner. 3 Do you see that? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: Yeah, you're 7 going a little fast here. Could 8 you just point me to where you're 9 reading from? 10 BY MR. SMITH: 11 Q. Sure. It's under -- it's 12 Page 11 of 12 under the conclusions. 13 A. Okay. Yeah. 14 Q. Do you see that? 15 A. Yes. 16 MR. SMITH: Do you want to 17 take a break, or do you want to go 18 on to a different section? 19 MR. FROST: If you're going 20 to move on to another section, 21 I'll use the restroom. 22 THE VIDEOGRAPHER: Off the 23 record. Time is 10:36. 24 (Short break.)</p>
<p style="text-align: right;">Page 115</p> <p>1 Do you see that? 2 MR. FROST: Objection to 3 form, the beginning of that 4 question. 5 BY MR. SMITH: 6 Q. Do you see that, Doctor? 7 A. I see it in the abstract, 8 yes. 9 Q. And then if we go -- that's 10 in Exhibit 13. 11 And if we go to Exhibit 14, 12 "Talc Occurrence, Characterization, and 13 Consumer Applications," and we go to what 14 Mr. Zazenski wrote in this publication, 15 also published in Regulatory Toxicology 16 and Pharmacology, his conclusion on Page 17 11 of 12. "Used for decades in a wide 18 variety of cosmetic and other 19 applications, talc has proven to be the 20 safest among all consumer products. 21 "A thorough review of the 22 literature provides no convincing 23 evidence that cosmetic talc when used as 24 intended presents any health risk to</p>	<p style="text-align: right;">Page 117</p> <p>1 THE VIDEOGRAPHER: We are 2 going back on record. Beginning 3 Media File Number 2. The time is 4 10:47. 5 BY MR. SMITH: 6 Q. Okay. Doctor, what are the 7 different histological types of ovarian 8 cancer? 9 A. There are four types. There 10 is invasive, the serous, which is the 11 most common, high grade, endometrioid, 12 clear cell, and mucinous. 13 Q. Do you know which type is 14 diagnosed most in the United States? 15 A. Yes. The first category of 16 the serous. 17 Q. Where do most experts 18 believe the histological type originates 19 in the human body? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: They don't 23 know. They are all derivatives of 24 epithelioid or epithelial cells.</p>

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<p style="text-align: right;">Page 118</p> <p>1 But it's unclear whether they have</p> <p>2 a common precursor or whether</p> <p>3 there are different precursors</p> <p>4 used for different histotypes.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. I'm talking about --</p> <p>7 specifically about serous. Do you</p> <p>8 understand that the large -- or do you</p> <p>9 understand that the large majority --</p> <p>10 vast majority of epithelial ovarian</p> <p>11 cancers diagnosed in the United States</p> <p>12 are serous type?</p> <p>13 A. Yes.</p> <p>14 Q. And my question to you is,</p> <p>15 do you know where scientists think that</p> <p>16 the serous type histological type of</p> <p>17 epithelial ovarian cancer originates?</p> <p>18 A. If you mean the site, it's</p> <p>19 thought that it originates in the</p> <p>20 fallopian tubes.</p> <p>21 Q. Peritoneal mesothelial cells</p> <p>22 line the peritoneal cavity, fallopian</p> <p>23 tubes, and ovaries of a woman, correct?</p> <p>24 A. They do, yes.</p>	<p style="text-align: right;">Page 120</p> <p>1 a risk factor on that mechanism as well?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: No. I think</p> <p>5 that that's an open-ended question</p> <p>6 on what the estrogen or the</p> <p>7 incessant ovulation does. I don't</p> <p>8 believe that it's linked to</p> <p>9 chronic inflammation, for example,</p> <p>10 in the ovary or in the fallopian</p> <p>11 tubes.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Okay.</p> <p>14 A. Or that has not been</p> <p>15 demonstrated.</p> <p>16 Q. In 2010, did IARC list talc</p> <p>17 as a possible carcinogen?</p> <p>18 MR. FROST: Objection to</p> <p>19 form.</p> <p>20 THE WITNESS: Yes. It</p> <p>21 listed talc, yes.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. And IARC in 2012 listed</p> <p>24 asbestos as a known human ovarian</p>
<p style="text-align: right;">Page 119</p> <p>1 Q. Do you have an opinion about</p> <p>2 what biological mechanisms or pathways</p> <p>3 can lead to ovarian cancer?</p> <p>4 A. I have an idea based upon</p> <p>5 what I have read and that is that there</p> <p>6 are certainly genetic predispositions</p> <p>7 that are associated with it. There</p> <p>8 certainly is an estrogen-dependent effect</p> <p>9 or incessant ovulation, but in terms of</p> <p>10 other causes, they aren't fully</p> <p>11 understood.</p> <p>12 Q. And what about incessant</p> <p>13 ovulation can lead to a woman contracting</p> <p>14 ovarian cancer?</p> <p>15 A. Incessant ovulation is</p> <p>16 thought to be important because it gives</p> <p>17 rise to estrogens that may influence the</p> <p>18 process of tumor development.</p> <p>19 Q. What about the rupture --</p> <p>20 the more than normal or abnormal rupture</p> <p>21 of incessant ovulation of the egg from</p> <p>22 the ovary and causing inflammation and</p> <p>23 injury chronically? Have you not read</p> <p>24 articles that base incessant ovulation as</p>	<p style="text-align: right;">Page 121</p> <p>1 carcinogen, correct?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: It did.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. And in 2010, in IARC, and on</p> <p>7 Prop 65, asbestiform talc is also a known</p> <p>8 human carcinogen. Are you familiar with</p> <p>9 that?</p> <p>10 A. No. You are going to have</p> <p>11 to refresh my on Prop 65.</p> <p>12 Q. Prop 65 is the</p> <p>13 classification in California. Are you</p> <p>14 familiar with that classification --</p> <p>15 A. I'm not familiar --</p> <p>16 Q. -- of hazardous substance?</p> <p>17 A. -- with the details of Prop</p> <p>18 65.</p> <p>19 Q. Okay.</p> <p>20 (Document marked for</p> <p>21 identification as Exhibit</p> <p>22 Mossman-15.)</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I'm going to attach as</p>

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<p>1 Exhibit 15, which is from OEHHA. It's</p> <p>2 the Prop 65 listing of talc containing</p> <p>3 asbestiform fibers. Have you seen that</p> <p>4 listing, Doctor, before?</p> <p>5 A. I have not.</p> <p>6 Q. Have you seen the IARC</p> <p>7 listing of talc-containing asbestiform</p> <p>8 fibers as a Group 1 carcinogen? Have you</p> <p>9 seen that before?</p> <p>10 A. Have I seen, you mean the</p> <p>11 monograph or --</p> <p>12 (Document marked for</p> <p>13 identification as Exhibit</p> <p>14 Mossman-16.)</p> <p>15 BY MR. SMITH:</p> <p>16 Q. Yes, I'm going to attach</p> <p>17 that as Exhibit 16.</p> <p>18 A. Okay.</p> <p>19 Q. Keep it. Have you seen that</p> <p>20 before?</p> <p>21 MR. FROST: Just for the</p> <p>22 record, because it's just a</p> <p>23 section of it, is this the -- the</p> <p>24 2010 talc monograph?</p>	<p>1 have my expert report in front of</p> <p>2 me.</p> <p>3 BY MR. SMITH:</p> <p>4 Q. In your -- I'm sorry --</p> <p>5 A. Like the jargon -- I'm</p> <p>6 sorry --</p> <p>7 Q. Go ahead.</p> <p>8 A. -- about the causation</p> <p>9 opinion. I -- I list several opinions.</p> <p>10 Q. I understand.</p> <p>11 A. But causation opinions, I'm</p> <p>12 not certain what you mean exactly.</p> <p>13 Q. I never saw a definitive</p> <p>14 opinion in your report that says talc</p> <p>15 does not cause ovarian cancer.</p> <p>16 MR. FROST: Objection to</p> <p>17 form.</p> <p>18 THE WITNESS: It -- it</p> <p>19 should have been conveyed as such.</p> <p>20 BY MR. SMITH:</p> <p>21 Q. Okay. And we'll get to your</p> <p>22 report in a minute.</p> <p>23 A. Okay.</p> <p>24 Q. Well, when did you arrive at</p>
Page 123	Page 125
<p>1 MR. SMITH: Yes. It should</p> <p>2 say it on the --</p> <p>3 MR. FROST: Yeah, it says</p> <p>4 talc on the top, but it's one of</p> <p>5 the --</p> <p>6 MR. SMITH: Yeah.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. Have you seen that before,</p> <p>9 Doctor?</p> <p>10 A. I have read this document,</p> <p>11 yes.</p> <p>12 Q. Okay. I looked at -- are</p> <p>13 all your opinions in this case contained</p> <p>14 in your report?</p> <p>15 A. I believe so. Yes.</p> <p>16 Q. And in your report, you</p> <p>17 don't give a causation opinion on</p> <p>18 cosmetic talc and ovarian cancer, do you?</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: You're --</p> <p>22 you're going to have to tell me</p> <p>23 what the causation opinion is</p> <p>24 specifically compared -- I don't</p>	<p>1 your opinions in this case? I mean I see</p> <p>2 the draft report was February 25, 2019,</p> <p>3 was when it's signed.</p> <p>4 Surely you came to your</p> <p>5 opinions before it was drafted?</p> <p>6 MR. FROST: Form.</p> <p>7 THE WITNESS: I did. I</p> <p>8 reviewed all the literature and</p> <p>9 came to my opinions before I</p> <p>10 drafted that report, which would</p> <p>11 have been probably at the end of</p> <p>12 December or in January of this</p> <p>13 year.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. Okay. So you're saying in</p> <p>16 your opinion, you give an opinion in your</p> <p>17 report that -- on cosmetic-grade talc and</p> <p>18 it causing ovarian cancer, or not causing</p> <p>19 ovarian cancer?</p> <p>20 MR. FROST: Objection to</p> <p>21 form.</p> <p>22 THE WITNESS: Yeah, I'd have</p> <p>23 to look at my opinions.</p> <p>24 BY MR. SMITH:</p>

32 (Pages 122 to 125)

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<p style="text-align: right;">Page 126</p> <p>1 Q. Hold on a second. Had you 2 formed that opinion in October 26th of 3 2018? 4 A. Which opinion, to answer? 5 Q. That talc, cosmetic-grade 6 talc does not cause ovarian cancer. 7 A. Yes. 8 Q. You weren't able to give me 9 that opinion in the Brower case. I 10 specifically asked you many, many times 11 and your counsel objected saying she does 12 not going to give a causation opinion. 13 She's not here to give a causation 14 opinion. Do you recall that? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yes, that 18 was -- that was before I reviewed 19 the scientific literature. 20 BY MR. SMITH: 21 Q. Well, I just asked you, did 22 you have that opinion on October 26, 2018 23 and you said you did. And that's when 24 you were deposed in Brower.</p>	<p style="text-align: right;">Page 128</p> <p>1 of her opinion that talc does not cause 2 ovarian cancer and I need to get to the 3 bottom of that. 4 He said, "Yeah, I understand 5 that. I'm trying to tell you that -- 6 that not going to ask her as a broad a 7 question as does talc cause ovarian 8 cancer based on all these entities. 9 We're going to ask her about her research 10 and what it means in terms of talc's 11 ability to cause the changes that can 12 lead to cancer, and then specifically the 13 testimony she's given previously 14 regarding her in vitro studies as well as 15 her review of animal studies dealing with 16 mesothelioma and talc, and testimony 17 she's given previously about cleavage 18 fragments, and then finally her opinions 19 and interpretation of Lauren 20 Plunkett's -- let me rephrase that. 21 The -- her comments on the interpretation 22 that Lauren Plunkett provided concerning 23 her studies as well as similar -- similar 24 studies."</p>
<p style="text-align: right;">Page 127</p> <p>1 MR. FROST: Objection. 2 THE WITNESS: Yeah, I'm not 3 sure what you mean about by my 4 opinion. My opinion has been 5 bolstered in terms of talc and 6 causation by reading since 7 October 18th. 8 BY MR. SMITH: 9 Q. I want to read on Page 66 of 10 the Brower deposition. 11 MR. FROST: Give me a 12 second. Let me catch up to you. 13 THE WITNESS: 66? Okay. 14 MR. FROST: Do you have 15 that, Brooke? 16 THE WITNESS: Hold on. I'm 17 almost there. 18 Okay. 19 BY MR. SMITH: 20 Q. And it goes -- it's 66 and 21 I'm going to go to Line 4. 22 "But that's not what she 23 said and nor has she retracted. There 24 are three things she relies for the basis</p>	<p style="text-align: right;">Page 129</p> <p>1 Has that changed, that 2 you're -- you're going to give an opinion 3 generally that talc does not cause 4 ovarian cancer from what your counsel 5 said you were going to do in October 26, 6 2018? 7 MR. FROST: Objection to 8 form. I just want to make the 9 record clear that Brower is 10 obviously different than the MDL 11 case. 12 MR. SMITH: I understand. 13 MR. FROST: But you can 14 answer. 15 BY MR. SMITH: 16 Q. Is -- is your report and 17 your testimony in this case different 18 than what you just -- what was said here? 19 A. It's not any different. I 20 think the emphasis is different, that I'm 21 relying upon my own research. But in 22 addition, since October 18th -- or 26, 23 2018, I have read the literature in terms 24 of the lack of migration of talc to the</p>

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<p>1 ovary. I've read the epidemiology. And</p> <p>2 I do have an opinion that is based upon</p> <p>3 the peer-reviewed scientific medical</p> <p>4 literature that talc is not associated</p> <p>5 with the causation of ovarian cancers.</p> <p>6 Q. Okay. We'll go specifically</p> <p>7 in your report in a minute. I just</p> <p>8 wanted to bring that question out right</p> <p>9 now.</p> <p>10 You cannot tell me what the</p> <p>11 risk factors for -- of ovarian cancer</p> <p>12 are, can you?</p> <p>13 A. The risk factors vary</p> <p>14 according to the epidemiological studies.</p> <p>15 Q. Do you consider talc a risk</p> <p>16 factor for ovarian cancer?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: If you are</p> <p>20 talking about a significant, it's</p> <p>21 not a simple yes or no answer.</p> <p>22 I would say that it -- talc</p> <p>23 is not a significant risk factor</p> <p>24 for ovarian cancer.</p>	<p>1 MR. SMITH: I'd like to</p> <p>2 attach this as the next numbered</p> <p>3 Exhibit 17.</p> <p>4 (Document marked for</p> <p>5 identification as Exhibit</p> <p>6 Mossman-17.)</p> <p>7 BY MR. SMITH:</p> <p>8 Q. It's a printout from the</p> <p>9 website, the University of Vermont</p> <p>10 Medical Center on ovarian cancer.</p> <p>11 And if you go to the second</p> <p>12 page, Doctor, it talks -- it has listed</p> <p>13 here the gynecological -- gynecologic</p> <p>14 oncology group with that organization.</p> <p>15 Do you see that on the front page?</p> <p>16 A. Yes. I don't know who -- I</p> <p>17 don't see any names listed.</p> <p>18 Q. And this is -- do you see at</p> <p>19 the top, University of Vermont Medical</p> <p>20 Center? Do you see that?</p> <p>21 A. I do.</p> <p>22 Q. And it has ovarian cancer</p> <p>23 listed at the top, correct, right under</p> <p>24 the heading? Right here.</p>
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<p>1 BY MR. SMITH:</p> <p>2 Q. That wasn't my question,</p> <p>3 Doctor. Is talc a risk factor for</p> <p>4 ovarian cancer?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: I think I just</p> <p>7 answered that, that it's not a</p> <p>8 simple yes or no.</p> <p>9 That the epidemiological</p> <p>10 studies indicate that it is not.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Are you an epidemiologist?</p> <p>13 A. No, but I certainly read the</p> <p>14 epidemiology.</p> <p>15 Q. So do you consider talc a</p> <p>16 risk factor for ovarian cancer?</p> <p>17 A. No, I don't.</p> <p>18 Q. Okay. You are affiliated</p> <p>19 with the University of Vermont Medical</p> <p>20 Center, aren't you?</p> <p>21 A. I am.</p> <p>22 Q. Is it a reputable</p> <p>23 organization?</p> <p>24 A. Yes.</p>	<p>1 A. Hold on here. Yes.</p> <p>2 Q. And if you flip to the</p> <p>3 second page, "Ovarian cancer, what you</p> <p>4 need to know." It says, "Ovarian cancer,</p> <p>5 what is it? Ovarian cancer risk</p> <p>6 factors." You see, "Age older than 55,</p> <p>7 obesity, reproductive history, family</p> <p>8 history of ovarian cancer, personal</p> <p>9 history of breast cancer, put talcum</p> <p>10 powder directly on genitals or sanitary</p> <p>11 napkins."</p> <p>12 Do you see that?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: Yeah, where is</p> <p>16 this? I'm sorry. Oh, I see it,</p> <p>17 okay.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. It's the third page. So you</p> <p>20 would disagree with the University of</p> <p>21 Vermont Medical Center on whether talc is</p> <p>22 a risk factor when put directly on the</p> <p>23 genitals and sanitary napkins for ovarian</p> <p>24 cancer?</p>

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<p style="text-align: right;">Page 134</p> <p>1 A. I rely, again, upon the 2 peer-reviewed scientific literature that 3 indicates certainly in cohort studies and 4 case-control studies that it is not a 5 risk factor in ovarian cancer. 6 MR. SMITH: I'm going to 7 object as nonresponsive. 8 BY MR. SMITH: 9 Q. Doctor, do you disagree with 10 the University of Vermont Medical Center 11 in this publication that lists risk 12 factors for ovarian cancer, and one 13 being, "Put talcum powder directly on 14 genitals or sanitary napkins"? 15 MR. FROST: Objection to 16 form. It's not a publication. 17 THE WITNESS: Yeah, and let 18 me emphasize that this isn't a -- 19 MR. SMITH: And I'm -- I've 20 just about had it. The speaking 21 objections are going to stop, or 22 I'm going to get the court in. 23 I'm -- this is the last one. Your 24 speaking objections --</p>	<p style="text-align: right;">Page 136</p> <p>1 disagree with the University of Vermont 2 Medical Center publication that I have in 3 front of you that's Exhibit 17, that 4 lists risk factors for ovarian cancer, 5 one being, "Put talcum powder directly on 6 genitals or sanitary napkins"? Do you 7 agree or disagree with that? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: I disagree 11 that that is a risk factor that's 12 significant. 13 BY MR. SMITH: 14 Q. Well, hold on. Wonder if 15 it's not significant. Do you believe 16 that talc is a risk -- an insignificant 17 risk factor? 18 A. I -- when you say 19 insignificant, I would -- I -- let me 20 qualify that these studies that I've read 21 in terms of the epidemiology show that it 22 is -- that the risks of talc are not 23 significant. 24 Q. So, there is some risk of</p>
<p style="text-align: right;">Page 135</p> <p>1 MR. FROST: Sure. I was 2 just -- 3 MR. SMITH: Object to form. 4 MR. FROST: I was just 5 making it clear to you what your 6 objection is so you can -- 7 MR. SMITH: I don't need it. 8 I don't need any speaking. I need 9 to form. And I'm done with it. 10 I've given you plenty of warnings. 11 BY MR. SMITH: 12 Q. Ma'am, do you disagree or 13 agree with what I printed off the website 14 of the University of Vermont Medical 15 Center on ovarian cancer risks? 16 A. I disagree that talcum 17 powder is a dose-related risk in ovarian 18 cancer based upon the peer-reviewed 19 scientific literature. 20 Q. Ma'am, that's -- 21 MR. SMITH: I'm going to 22 object to nonresponsiveness. 23 BY MR. SMITH: 24 Q. Again, do you agree or</p>	<p style="text-align: right;">Page 137</p> <p>1 talc applied to the genitals in its 2 relation to ovarian cancer. You just say 3 it's small. 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: No. I'm 7 saying it's insignificant in the 8 scientific peer-reviewed 9 literature. 10 BY MR. SMITH: 11 Q. Well, what do you define as 12 insignificant? Because any risk to me of 13 getting one of the most deadly forms of 14 cancer, any risk at all that has -- on a 15 product that has no health benefit is 16 significant to me. So we could be 17 defining significant and insignificant in 18 different terms. 19 So are you saying that there 20 is some risk, albeit small, of genital 21 application of talc and ovarian cancer? 22 MR. FROST: Objection to 23 form. 24 THE WITNESS: I am speaking</p>

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<p>1 from a scientist who has looked at 2 the risk, relative risks, in 3 cohort studies and all of these 4 indicate that talcum powder is not 5 a significant risk in ovarian 6 cancer causation. 7 BY MR. SMITH: 8 Q. Well, when you say 9 significant -- not a significant risk, 10 it's still -- your answer implies that 11 there is still some risk, okay. 12 My question to you is, 13 however small or however significant or 14 not, is there some risk in its -- in the 15 application -- genital application of 16 talc and the risk of ovarian cancer? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: All I'm saying 20 is that no, it's not a simple yes 21 or no answer, that as a scientist, 22 looking at the literature, that 23 talc powder is not a statistically 24 significant risk factor in the</p>	<p>1 epidemiology primarily. 2 BY MR. SMITH: 3 Q. Ma'am I'm going to need you 4 to be more specific. We're here to get 5 your opinions. I don't need 6 generalities. 7 MR. FROST: I'm going to say 8 Okay. She's -- you've got to let 9 her finish her answer. She's 10 going to follow up. 11 THE WITNESS: So let's talk 12 about -- I have three reasons for 13 that statement, the first and most 14 important being the epidemiology; 15 that is, the cohort studies, all 16 of the four, looking at thousands 17 of individuals, do not indicate 18 that talcum powder is a risk in 19 the development of ovarian cancer, 20 and they state it as such. 21 I also would base -- 22 BY MR. SMITH: 23 Q. Well -- okay. I'm going 24 to -- I want to -- let's just break each</p>
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<p>1 causation of ovarian cancer. 2 BY MR. SMITH: 3 Q. What do you base that on? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: All right. Do 7 you want me to start with my 8 opinions? 9 BY MR. SMITH: 10 Q. I want to know what you base 11 that statement on. 12 A. Okay. 13 Q. I don't need your opinions. 14 I know what they are. We're going to get 15 to them. I need to know what do you base 16 that the genital application of talc by a 17 woman in the epidemiological studies does 18 not provide or show a statistically 19 significant increased risk of ovarian 20 cancer? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: Again, I can 24 emphasize that it's based on</p>	<p>1 one down specifically. 2 A. Okay. 3 Q. All of those cohort studies 4 find a non-statistical increased risk, 5 correct? 6 MR. FROST: Objection to 7 form. 8 THE WITNESS: Again, if it's 9 not statistical, it can be chance. 10 We're talking about a risk less 11 than twofold, and in the field of 12 epidemiology and in the field of 13 biology in general, one looks at a 14 risk or a relative risk and it 15 generally becomes significant when 16 it's above two. 17 None of those studies show 18 an observed risk or relative risk 19 of greater than two. 20 BY MR. SMITH: 21 Q. So you're saying to have a 22 substance be a risk factor for causing 23 disease, that you need a relative risk in 24 the epidemiology of 2.0 or higher?</p>

<p style="text-align: right;">Page 142</p> <p>1 A. In general, but you also can 2 exclude risks that are lower than that if 3 they aren't statistically significant. 4 Q. Do you understand that 5 statistical significance in some of those 6 cohort studies might be because they did 7 not have enough people to power the 8 study? 9 MR. FROST: Objection. 10 BY MR. SMITH: 11 Q. Have you looked at any of 12 that? 13 MR. FROST: Objection to 14 form. 15 THE WITNESS: I'm not -- I'm 16 not an epidemiologist. I'm not 17 going to go into the shortcomings 18 of these studies. But there are 19 thousands of individuals and they 20 did have the power to detect other 21 risk factors such as genetic 22 susceptibility. 23 BY MR. SMITH: 24 Q. Well, do you know whether or</p>	<p style="text-align: right;">Page 144</p> <p>1 exposure history, or did the cohort 2 studies just look at frequency or just 3 look at duration? Do you know? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: I -- again I'd 7 have to go back. If you've got a 8 copy of the studies I'd be happy 9 to comment on that. 10 BY MR. SMITH: 11 Q. Well, let me ask you a 12 question. To get an accurate exposure 13 history, wouldn't you agree with me that 14 you need both frequency and duration to 15 get the most accurate exposure history in 16 a woman? 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: Yeah. That 20 would be a question for an 21 epidemiologist. 22 I can't comment on the 23 relative importance of frequency, 24 duration, or dose.</p>
<p style="text-align: right;">Page 143</p> <p>1 not these cohorts assessed whether they 2 were genital talc users at one period and 3 followed up to see if they continued as 4 chronic users, or did they just ask them 5 at one point in time? 6 MR. FROST: Objection to 7 form. 8 THE WITNESS: I cannot go 9 through the details. All I can 10 tell you is the bottom lines of 11 these studies. 12 They had fairly reputable 13 talc histories. And they did not 14 show either a statistical increase 15 in relative risk, but they also 16 did not show that there was 17 consistency or dose-response based 18 on frequency or duration. And 19 those are other important 20 variables to consider. 21 BY MR. SMITH: 22 Q. Do you know if any of these 23 studies took into account frequency and 24 duration to get an actual -- accurate</p>	<p style="text-align: right;">Page 145</p> <p>1 BY MR. SMITH: 2 Q. Okay. So if I asked you how 3 many times a year you used genital talc, 4 and you told me how many times a year, 5 you -- you said -- excuse me. 6 How frequently you used 7 talc, and you said twice a week. How 8 would I ever know what the applications 9 were in a year if I don't know the 10 duration? 11 MR. FROST: Objection to 12 form. 13 THE WITNESS: Yeah, that's a 14 question for an epidemiologist. I 15 don't have the actual 16 questionnaires that were provided 17 in these studies. 18 But at the time they were 19 the best questionnaires that could 20 be gleaned in terms of personal 21 history of use. 22 BY MR. SMITH: 23 Q. So you are relying on the 24 cohorts for your opinion on the</p>

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<p style="text-align: right;">Page 146</p> <p>1 epidemiological cohort studies that talc 2 does not significantly increase the risk 3 of ovarian cancer. You cannot tell me in 4 the cohorts how many times they asked the 5 question of -- if these women are genital 6 talc users or followed up to see if they 7 were genital talc users, correct? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: Again, I'd 11 have to look at the studies. I've 12 read them. I can't recall. There 13 are four of them. And I can't 14 recall whether the questionnaire 15 information was in detail in those 16 publications. 17 The important point is that 18 regardless of the questionnaire, 19 and the talc use that was 20 documented, there was not an 21 increase in dose-response or 22 frequency which gives additional 23 weight to the epidemiology that is 24 the relative risk that talc</p>	<p style="text-align: right;">Page 148</p> <p>1 form. 2 THE WITNESS: Yeah, I -- 3 again, I would have to look at 4 those studies. I don't recall the 5 details. But they attempted to do 6 frequency and dose-response in the 7 studies. 8 BY MR. SMITH: 9 Q. Can you tell me if they 10 allowed for an adequate latency period or 11 follow-up period for the women for a 12 latency -- latent injury and disease like 13 ovarian cancer, do you know if they 14 allowed for an adequate exposure -- 15 latency exposure period? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yeah, 19 certainly the follow-up studies in 20 the Nurses' Health Study did. And 21 since we don't know the latency of 22 development, we -- I can't really 23 answer that question. 24 BY MR. SMITH:</p>
<p style="text-align: right;">Page 147</p> <p>1 doesn't cause ovarian cancer. 2 BY MR. SMITH: 3 Q. Well, if you're going to use 4 dose-response as one of the factors that 5 you're -- in these cohorts that you're 6 relying on to say that talc does not 7 significantly increase the risk of 8 ovarian cancer, and you can't tell me 9 whether these studies looked at frequency 10 and duration to get an accurate exposure 11 history, that would all factor in to 12 whether you get a dose-response 13 relationship is a little baffling. 14 Do you know whether or not 15 that these four cohort studies that 16 you're relying on, based on lack of 17 dose-response, that talc is not a 18 significant increased risk of ovarian 19 cancer, whether or not all four studies 20 looked at both frequency and duration to 21 get an accurate exposure history that 22 would relate to an adequate dose-response 23 answer to the question? 24 MR. FROST: Objection to</p>	<p style="text-align: right;">Page 149</p> <p>1 Q. So that's -- what else do 2 you rely on to say that talc doesn't 3 significantly increase the risk of 4 ovarian cancer? 5 A. The fact that there have 6 been many animal studies, including those 7 that have injected talc directly into the 8 ovary and those have not given rise to 9 ovarian cancers or mesotheliomas. 10 Q. Did they show adverse 11 cellular changes? 12 A. You'll have to define 13 adverse cellular change. 14 Q. Did they show a reaction to 15 talc? 16 A. I'm sure they must have. 17 Q. Did you look at any other 18 epidemiological studies besides the 19 cohorts to arrive at your opinion that 20 talc does not significantly increase the 21 risk of ovarian cancer? 22 A. Yes. I looked at the 23 case-control studies of which I believe 24 two out of -- I think there are at least</p>

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<p>1 14 or maybe even more, probably between 2 14 and 20 studies, on the majority of 3 those did not show significant risks. 4 And none of them showed an increase with 5 frequency or dose of talc. 6 Q. Did not show a significant 7 increase in risk. 8 A. Mm-hmm. 9 Q. You mean the majority of 10 them did not show a statistical 11 significant increased risk of -- for 12 ovarian cancer? 13 A. The majority of them did not 14 show a statistically significant risk for 15 ovarian cancer that was related to dose 16 and duration of exposure. 17 Q. Well, hold on a second. 18 Let's -- dose-response is totally 19 separate from whether you -- you find a 20 statistically significant increased risk 21 of ovarian cancer from genital talc use 22 in a case-control study. Let's break it 23 down. 24 You're saying the majority</p>	<p>1 A. I haven't looked at them? 2 Q. Any post 2010 animal 3 experience -- experiments. I asked you 4 that in Brower. Had you looked at any -- 5 we talked about IARC in 2010, the 6 monograph. 7 A. Right. 8 Q. And you'd said you had not 9 looked at any animal studies post that 10 monograph; is that correct? 11 A. That had been published 12 since 2010. 13 Q. Yes. 14 A. Correct. 15 Q. And if the monograph is 16 published in 2010, you realize that most 17 of those studies occurred well before 18 2010? 19 A. Yes. 20 Q. Dr. Saenz, is she an 21 epidemiologist? 22 A. I believe that she is an 23 oncologist. 24 Q. Okay. So you relied on the</p>
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<p>1 of the case-control studies did not show 2 a statistically significant increased 3 risk of ovarian cancer from genital talc 4 use? 5 A. Yes. 6 Q. Okay. 7 MR. FROST: Objection to 8 form. 9 BY MR. SMITH: 10 Q. What other epidemiological 11 studies did you look at? Any? 12 A. I looked at the summary of 13 the reports by Dr. Saenz and Dr. Diette 14 which covered these beautifully. So my 15 opinions are certainly bolstered by their 16 reports. 17 Q. So your opinions are 18 bolstered by two defense experts? 19 A. That is after I wrote my 20 report. So my original observations are 21 based on epidemiology and animal 22 experiments and mechanistic studies. 23 Q. You haven't looked at any 24 animal experiments since 2010, right?</p>	<p>1 summary or giving credibility, you said, 2 or I don't know what term you used. 3 Bolstered your opinion by Dr. Saenz who 4 is a gynecological oncologist on the 5 epidemiology. 6 MR. FROST: Objection to 7 form. 8 BY MR. SMITH: 9 Q. Is that correct? 10 A. Yes. I think she gave a 11 very cogent review, and also I believe 12 Dr. Diette, I read his expert report and 13 he gives a, again, I feel a balanced, 14 good overview of the strengths and 15 weaknesses of the studies. 16 Q. Did you do an independent 17 review of the strengths and weaknesses of 18 every epidemiological study that you just 19 discussed, that being the case-control 20 studies and the cohorts? 21 MR. FROST: Objection. 22 THE WITNESS: I did before I 23 wrote my report. I didn't cover 24 it in my report. I looked at</p>

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<p style="text-align: right;">Page 154</p> <p>1 these studies, however. I read</p> <p>2 them, and I looked at their</p> <p>3 abstracts as well for their</p> <p>4 significance.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. What basis do you have to</p> <p>7 rely on the strengths and weaknesses of</p> <p>8 epidemiological study when you say you're</p> <p>9 not an epidemiologist or not an expert in</p> <p>10 epidemiology?</p> <p>11 MR. FROST: Object to form.</p> <p>12 THE WITNESS: Epidemiology</p> <p>13 is something throughout the years</p> <p>14 that I've had to comment upon in</p> <p>15 all of my published materials in</p> <p>16 trying to make correlations</p> <p>17 between what I observe and what's</p> <p>18 been observed in epidemiology.</p> <p>19 So I am not one to question</p> <p>20 or critique the studies in terms</p> <p>21 of their individual positive or</p> <p>22 negative features. But all the</p> <p>23 studies say the same thing,</p> <p>24 especially the cohort studies.</p>	<p style="text-align: right;">Page 156</p> <p>1 specific strengths and weaknesses of the</p> <p>2 Nurses' Health studies that you examined</p> <p>3 to give weight or non-weight to those</p> <p>4 particular cohort studies.</p> <p>5 A. Okay.</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: So I'm going</p> <p>9 to give two without going back to</p> <p>10 the papers, which aren't in front</p> <p>11 of me.</p> <p>12 There would not be the</p> <p>13 issues of recall bias in those</p> <p>14 studies as there would have been</p> <p>15 in case-control studies.</p> <p>16 And there would not have</p> <p>17 been misclassification of tumors</p> <p>18 because these are prospective</p> <p>19 studies.</p> <p>20 Other than that, I could not</p> <p>21 comment unless I have the study in</p> <p>22 front of me.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. That -- your statement that</p>
<p style="text-align: right;">Page 155</p> <p>1 BY MR. SMITH:</p> <p>2 Q. Well, if you're going to</p> <p>3 give weight to certain evidence and not</p> <p>4 weight to certain evidence to arrive at</p> <p>5 an opinion, and you're not -- you're not</p> <p>6 specifically look -- and are able to look</p> <p>7 at the strengths and weaknesses of these</p> <p>8 epidemiological studies, how do you</p> <p>9 arrive at an opinion about the</p> <p>10 epidemiological studies in general?</p> <p>11 MR. FROST: Objection to</p> <p>12 form.</p> <p>13 THE WITNESS: As I</p> <p>14 emphasize, I look at the relative</p> <p>15 risk. I look at whether there's a</p> <p>16 dose-response relationship in</p> <p>17 terms of talc use. And there are</p> <p>18 no other conclusions from these</p> <p>19 studies that I can make other than</p> <p>20 talcum powder does not pose a risk</p> <p>21 that's significant in the</p> <p>22 development of ovarian cancers.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I would like to know the</p>	<p style="text-align: right;">Page 157</p> <p>1 you just made is a statement that could</p> <p>2 be made generally about any cohort versus</p> <p>3 case-control study, correct?</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: You'd have to</p> <p>6 ask an epidemiologist about that.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. I want to know the specific</p> <p>9 shortcomings of the Nurses' Health</p> <p>10 studies and the other two cohort studies</p> <p>11 that you considered before giving any</p> <p>12 weight to those studies for your opinion</p> <p>13 that talc does not significantly increase</p> <p>14 the risk of ovarian cancer?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Again, I did</p> <p>17 not see specific weaknesses in</p> <p>18 those studies.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Okay. Can talc be safely</p> <p>21 absorbed in a woman's vagina?</p> <p>22 A. I don't think there's any</p> <p>23 evidence for talc absorption in a vagina.</p> <p>24 MR. FROST: What number are</p>



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<p style="text-align: right;">Page 158</p> <p>1 we on?</p> <p>2 MR. SMITH: 18.</p> <p>3 (Document marked for</p> <p>4 identification as Exhibit</p> <p>5 Mossman-18.)</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Have you ever seen any</p> <p>8 internal documents of the defendants, of</p> <p>9 Johnson &amp; Johnson, Imerys, Luzenac?</p> <p>10 A. I have not.</p> <p>11 Q. Have you asked to see any of</p> <p>12 them?</p> <p>13 A. No.</p> <p>14 Q. Would you like to have seen</p> <p>15 any of them?</p> <p>16 A. I wouldn't know what to ask</p> <p>17 for.</p> <p>18 Q. Well, if they're scientific</p> <p>19 and otherwise -- documents from the</p> <p>20 company that you're defending from</p> <p>21 scientists from the company, would you</p> <p>22 have liked to have seen those?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>	<p style="text-align: right;">Page 160</p> <p>1 bottom right there's a Bates number. It</p> <p>2 says J&amp;J, and it's got some numbers. And</p> <p>3 that's just to indicate that they</p> <p>4 produced this to me.</p> <p>5 And what this document is,</p> <p>6 Doctor, it's about a cornstarch</p> <p>7 substitute that they were looking at in</p> <p>8 testing. And I want to go to the last</p> <p>9 page. It's called it's called a Dry Flo</p> <p>10 product. And in the second paragraph,</p> <p>11 "Since the meeting, Ashton</p> <p>12 established" -- and he is an employee of</p> <p>13 Johnson &amp; Johnson -- "the largest</p> <p>14 commercial use of Dry-Flo are in vitamin</p> <p>15 A manufacturer (5 percent in finished</p> <p>16 product) and as a condom lubricant where</p> <p>17 it had replaced talc because it was found</p> <p>18 to be safely absorbed in the vagina,</p> <p>19 whereas of course talc was not."</p> <p>20 Do you have an opinion</p> <p>21 whether talc can be safely absorbed in a</p> <p>22 woman's vagina?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>
<p style="text-align: right;">Page 159</p> <p>1 THE WITNESS: Yeah, I can't</p> <p>2 think of specific instances.</p> <p>3 Again, I'm not looking at internal</p> <p>4 documents to render my opinions.</p> <p>5 I'm looking at the peer-reviewed</p> <p>6 literature.</p> <p>7 BY MR. SMITH:</p> <p>8 Q. This is an article --</p> <p>9 actually, it's an internal memo from</p> <p>10 Johnson &amp; Johnson. You see the title</p> <p>11 is -- subject is "Cornstarch</p> <p>12 development." Would you agree with me</p> <p>13 that cornstarch powder, there's no</p> <p>14 reported ill effects of cornstarch powder</p> <p>15 and ovarian cancer risk?</p> <p>16 A. I have not seen that in the</p> <p>17 literature. But I have not done a review</p> <p>18 of cornstarch through PubMed.</p> <p>19 Q. You see, "Cornstarch</p> <p>20 development, February 21st, 1964," at the</p> <p>21 top.</p> <p>22 Do you see that?</p> <p>23 A. I do.</p> <p>24 Q. And if you look at the</p>	<p style="text-align: right;">Page 161</p> <p>1 BY MR. SMITH:</p> <p>2 Q. I think you stated earlier.</p> <p>3 I thought you said that you couldn't see</p> <p>4 any reason why it couldn't be.</p> <p>5 MR. SMITH: Could we go back</p> <p>6 to that question?</p> <p>7 THE WITNESS: I don't know</p> <p>8 what they mean by absorbed safely</p> <p>9 in the vagina. Talc enters and</p> <p>10 other things enter cells. They're</p> <p>11 not absorbed. So I have -- I'm</p> <p>12 not sure what the scientific</p> <p>13 information is here.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. If you believe that talc</p> <p>16 could be safely absorbed in a woman's</p> <p>17 vagina, you would be in disagreement with</p> <p>18 Mr. Ashton that wrote this letter on</p> <p>19 February 21, 1964, as an employee of</p> <p>20 Johnson &amp; Johnson, correct?</p> <p>21 MR. FROST: Objection to</p> <p>22 form.</p> <p>23 THE WITNESS: Yeah, I have</p> <p>24 not -- I can't comment on this,</p>

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<p style="text-align: right;">Page 162</p> <p>1 because I'm unaware of any studies</p> <p>2 with either cornstarch or talc</p> <p>3 absorption in the vagina. I don't</p> <p>4 know what that means.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Can talc cause inflammation?</p> <p>7 MR. FROST: Objection to</p> <p>8 form.</p> <p>9 THE WITNESS: Again, it</p> <p>10 depends upon the circumstances and</p> <p>11 the dose and the site of</p> <p>12 application.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Can talc cause inflammation?</p> <p>15 MR. FROST: Objection to</p> <p>16 form.</p> <p>17 THE WITNESS: Yeah. You'd</p> <p>18 have to ask me in terms of the</p> <p>19 dose or give me an example.</p> <p>20 BY MR. SMITH:</p> <p>21 Q. Is talc capable of causing</p> <p>22 inflammation in human tissue?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>	<p style="text-align: right;">Page 164</p> <p>1 broadest sense. It would depend</p> <p>2 upon the dose, duration from the</p> <p>3 oxidant stress.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. Do you have an opinion on</p> <p>6 whether inhaled particles can reach the</p> <p>7 ovaries?</p> <p>8 A. That has not been shown.</p> <p>9 So no one has really looked</p> <p>10 at that in detail. But the answer is</p> <p>11 that most of the information suggests</p> <p>12 that an inhaled particle is dealt with</p> <p>13 locally, rather than disseminated.</p> <p>14 Although there's evidence in the</p> <p>15 bloodstream that there is dissemination</p> <p>16 of materials throughout the body.</p> <p>17 Q. Have you ever conducted a</p> <p>18 study on cosmetic talc and ovarian</p> <p>19 cancer?</p> <p>20 A. I haven't used cosmetic</p> <p>21 talc, as I've said previously.</p> <p>22 Q. Have you ever published on</p> <p>23 asbestos and ovarian cancer?</p> <p>24 A. No. But I've published</p>
<p style="text-align: right;">Page 163</p> <p>1 THE WITNESS: In human</p> <p>2 tissue? It's been used in</p> <p>3 pleurodesis if that's what you're</p> <p>4 talking about, which induces an</p> <p>5 acute inflammation that's</p> <p>6 beneficial to patients with</p> <p>7 malignant effusions.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. Can chronic inflammation</p> <p>10 lead to ovarian cancer?</p> <p>11 MR. FROST: Objection to</p> <p>12 form.</p> <p>13 THE WITNESS: There is no</p> <p>14 evidence that it's linked to</p> <p>15 causation.</p> <p>16 So I can't comment on that.</p> <p>17 It hasn't been shown.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Can oxidative stress lead to</p> <p>20 ovarian cancer?</p> <p>21 MR. FROST: Objection to</p> <p>22 form.</p> <p>23 THE WITNESS: Yeah, I</p> <p>24 couldn't agree with that in the</p>	<p style="text-align: right;">Page 165</p> <p>1 studies on asbestos, on ovarian</p> <p>2 epithelial cells.</p> <p>3 Q. Have you ever published on</p> <p>4 asbestos and ovarian cancer?</p> <p>5 MR. FROST: Objection to</p> <p>6 form.</p> <p>7 THE WITNESS: Yeah, I did</p> <p>8 state, and I believe it's in the</p> <p>9 Shukla and Hillegass paper,</p> <p>10 references on ovarian cancer and</p> <p>11 asbestos.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Can you turn to the Brower</p> <p>14 deposition Page 134?</p> <p>15 A. Mm-hmm.</p> <p>16 Q. Line 10.</p> <p>17 "Question: Have you ever</p> <p>18 conducted a study on asbestos and ovarian</p> <p>19 cancer?"</p> <p>20 "Answer: No."</p> <p>21 Has that changed since</p> <p>22 October of 2000 --</p> <p>23 A. I'm sorry, could you point</p> <p>24 that out again?</p>

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<p style="text-align: right;">Page 166</p> <p>1 Q. Sure. Line 10, on Page 134.</p> <p>2 "Question: Have you ever</p> <p>3 conducted a study on asbestos and ovarian</p> <p>4 cancer?"</p> <p>5 And what was your answer?</p> <p>6 A. No. I haven't looked at</p> <p>7 ovarian cancer, per se.</p> <p>8 Q. Can I rely on that testimony</p> <p>9 in Brower as being accurate?</p> <p>10 A. Pardon me?</p> <p>11 Q. Can I rely on the testimony</p> <p>12 in this Brower case that I just read as</p> <p>13 being accurate?</p> <p>14 A. Yes. I've not looked at --</p> <p>15 at asbestos and ovarian cancer. I</p> <p>16 emphasize that I've looked at asbestos</p> <p>17 effects on ovarian epithelial case.</p> <p>18 Q. Have you ever given a speech</p> <p>19 or seminar on talc and ovarian cancer?</p> <p>20 A. No.</p> <p>21 Q. Have you ever done --</p> <p>22 conducted a study on fibrous talc and its</p> <p>23 carcinogenicity related to ovarian</p> <p>24 cancer?</p>	<p style="text-align: right;">Page 168</p> <p>1 Q. Have you ever conducted a</p> <p>2 study on EMPs and ovarian cancer?</p> <p>3 A. Again, I haven't used</p> <p>4 ovarian cancer cells, just ovarian</p> <p>5 epithelial cells that develop into</p> <p>6 cancer.</p> <p>7 Q. And EMPs can cause</p> <p>8 epigenetic changes in human cells that</p> <p>9 may lead to cancer, correct?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Again, it</p> <p>13 depends on the EMP. That's true</p> <p>14 for amphibole asbestos fibers.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. Well, it's true for any</p> <p>17 elongated mineral particle, correct?</p> <p>18 A. What --</p> <p>19 Q. Not just asbestos?</p> <p>20 A. That does what?</p> <p>21 Q. That cause can give rise to</p> <p>22 epigenetic changes in human cells that</p> <p>23 may lead to cancer.</p> <p>24 A. No. There are other --</p>
<p style="text-align: right;">Page 167</p> <p>1 A. You're going to have to be</p> <p>2 specific. When you talk about ovarian</p> <p>3 cancer studies, are you talking about</p> <p>4 studies on ovarian epithelial cells or</p> <p>5 are you talking about studies on cancer</p> <p>6 cells?</p> <p>7 Q. Can you look at Page 136 of</p> <p>8 your Brower testimony?</p> <p>9 A. Sure.</p> <p>10 Q. Line 4. "And you've never</p> <p>11 conducted a study on fibrous talc and its</p> <p>12 carcinogenicity to ovarian cancer,</p> <p>13 correct?"</p> <p>14 "Answer: I have not used</p> <p>15 ovarian cells in studies with fibrous</p> <p>16 talcs."</p> <p>17 Is that still true today?</p> <p>18 A. Yes. Fibrous talcs have not</p> <p>19 been evaluated in ovarian epithelial</p> <p>20 cells.</p> <p>21 Q. Have you ever conducted a</p> <p>22 study on asbestos in talc and ovarian</p> <p>23 cancer?</p> <p>24 A. No.</p>	<p style="text-align: right;">Page 169</p> <p>1 there are materials that we and others</p> <p>2 have used as negative controls in our</p> <p>3 studies that are fibrous and are EMPs</p> <p>4 that don't give rise to precancerous</p> <p>5 changes.</p> <p>6 Q. Have you ever conducted a</p> <p>7 study on heavy metals and ovarian cancer?</p> <p>8 A. I haven't.</p> <p>9 Q. Can you give an opinion on</p> <p>10 whether heavy metals contribute to cause</p> <p>11 ovarian cancer?</p> <p>12 A. Yes. I have not seen any</p> <p>13 studies where heavy metals have given</p> <p>14 rise to ovarian cancers in animals.</p> <p>15 Q. You're saying there are no</p> <p>16 studies on heavy metals and ovarian</p> <p>17 cancer risk?</p> <p>18 A. I --</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: The -- I have</p> <p>22 not seen any studies that have</p> <p>23 given rise to ovarian cancers.</p> <p>24 There are many studies with</p>

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<p style="text-align: right;">Page 170</p> <p>1 animals using heavy metals at a 2 variety of high concentrations and 3 methods of injection or 4 inhalation. And these have not 5 given rise to ovarian cancers. 6 BY MR. SMITH: 7 Q. What about, do you have an 8 opinion whether fibrous talc can cause 9 ovarian cancer? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Based upon my 13 research with lung epithelial 14 cells, I would argue against that 15 being a true statement. 16 BY MR. SMITH: 17 Q. So you are extrapolating 18 your studies on lung cells to whether 19 fibrous talc can cause ovarian cancer? 20 A. I'm not extrapolating. I'm 21 saying that fibrous talcs as evaluated in 22 my studies and in animal studies have not 23 given rise to ovarian cancers. 24 Q. You would --</p>	<p style="text-align: right;">Page 172</p> <p>1 If they were relevant to 2 ovarian epithelial cells, I would have 3 seen responses to these materials in my 4 studies. 5 Q. But you've never tested 6 ovarian cells for that? 7 A. No. But as I emphasize, 8 I've got -- I've gotten the same 9 responses in lung epithelial and 10 mesothelial cells. So there's different 11 cell types that are important. 12 Again, epithelial cells are 13 the cells that give rise to cancers. So 14 ovarian epithelial cells are probably 15 very similar in their responses to lung 16 epithelial cells. 17 Q. Probably? What are you 18 basing that on? Probably? 19 MR. FROST: Objection. 20 THE WITNESS: Yeah, I'm 21 basing it on historical studies 22 with asbestos fibers that have 23 shown the same pre-neoplastic 24 effects in our laboratory, in</p>
<p style="text-align: right;">Page 171</p> <p>1 A. So that would argue against 2 the connection. 3 Q. Do you know whether fibrous 4 talc or other minerals act differently in 5 pleural cells versus ovarian cells or 6 peritoneal cells? 7 MR. FROST: Objection to 8 form. 9 THE WITNESS: No, they turn 10 on the same signaling pathways in 11 lung epithelial cells and 12 mesothelial cells. 13 BY MR. SMITH: 14 Q. Do you know whether or not 15 fiber dimensions, crystalline structures, 16 shape tensile strength of asbestos, have 17 any relevance to ovarian cancer? 18 A. Could we go through these 19 one at a time? 20 Q. Sure. 21 A. So, I would argue that these 22 different properties are properties of 23 asbestos fibers that have given rise to 24 mesotheliomas or lung cancers.</p>	<p style="text-align: right;">Page 173</p> <p>1 other laboratories that have 2 looked at a host or a huge range 3 of different cell types. And the 4 basic phenomena, the properties of 5 those asbestos fibers are the same 6 in terms of their biological 7 reactivity in a host of different 8 cell types. 9 BY MR. SMITH: 10 Q. But you've never done that 11 with ovarian cancer cells, right? 12 A. I have -- 13 Q. Ovarian cells, excuse me. 14 A. Yeah. 15 Q. You have not done that with 16 ovarian cells? 17 A. I have only looked at 18 fibrous -- I should say non-fibrous talc 19 in ovarian epithelial cells. 20 Q. And when we were talking 21 about fibrous talc earlier, you've never 22 done any studies on fibrous talc correct? 23 A. I had done studies on 24 fibrous talcs.</p>

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<p style="text-align: right;">Page 174</p> <p>1 Q. The one study in New York, 2 correct? 3 A. The study with Dr. Wiley 4 where we looked in two different cell 5 types at three different preparations of 6 fibrous talcs. 7 Q. Is crystalline silica a 8 fibrogenic dust that causes oxidative 9 damage to cells? 10 A. It does at very high 11 concentrations. 12 Q. Have you ever performed 13 rodent studies on talc? 14 A. I have not. 15 Q. You've never performed any 16 rodent inhalation studies on talc and its 17 relation to ovarian cancer; is that true? 18 A. I have not performed the 19 studies. 20 Q. Same for cleavage fragments? 21 A. I have not used cleavage 22 fragments in rodent inhalation studies. 23 Q. You've not performed studies 24 on whether or not a▯bestos cleavage</p>	<p style="text-align: right;">Page 176</p> <p>1 What do you base that on? 2 A. The fact that Zazenski and 3 others describe it as cosmetic and 4 pharmaceutical tales are 98 percent pure 5 as opposed to industrial tales from the 6 mining sites. 7 Q. You're relying on Zazenski, 8 who was an employee of Imerys, who is 9 involved in talc litigation, who 10 published in the Regulatory Toxicology 11 and Pharmacology publication that we 12 discussed earlier? 13 MR. FROST: Objection to 14 form. 15 THE WITNESS: That's only 16 one paper. I believe that this is 17 summarized in IARC 2010. It says 18 the exact same thing. 19 BY MR. SMITH: 20 Q. Well, hold on. You said you 21 hadn't seen any internal documents. 22 Where are you seeing the Zazenski stuff? 23 A. Zazenski is a paper that I 24 pulled from the literature in a</p>
<p style="text-align: right;">Page 175</p> <p>1 fragments cause ovarian cancer, correct? 2 A. I have not looked at 3 cleavage fragments in ovarian epithelial 4 cells, that's correct. 5 Q. And you do not know whether 6 the biodurability of asbestos or talc 7 have any relevance to the development of 8 ovarian cancer, correct? 9 A. That hasn't been examined 10 since we don't know the latency period of 11 ovarian cancers to begin with. 12 Q. Do you know what Baby Powder 13 is made of? 14 MR. FROST: Objection to 15 form. 16 THE WITNESS: Yeah. I -- I 17 believe it's indicated as such on 18 the label. 19 In general, yes. I'm aware 20 that it has some fragrance 21 chemicals, but it's also a very 22 pure type of talc. 23 BY MR. SMITH: 24 Q. A very pure type of talc.</p>	<p style="text-align: right;">Page 177</p> <p>1 peer-reviewed journal. 2 Q. The Regulatory Toxicology 3 and Pharmacology -- 4 A. Talked about -- yes. 5 Q. -- publication? 6 A. Yes. That's one source. 7 IARC also summarizes the 8 properties of tales in its monograph in 9 several places in the 2010 document. And 10 has additional references. 11 Q. What is Shower to Shower 12 made of? 13 A. I would have to look at the 14 label. 15 Q. Do you know? 16 A. I don't. 17 Q. Do you know what percentage 18 of Baby Powder is talc and what is 19 other -- other constituents? 20 A. I don't know the percentage 21 values. 22 Q. None of your studies 23 concerned Baby Powder or Shower to 24 Shower, correct?</p>

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<p>Page 178</p> <p>1 A. I have not used those 2 specifically. 3 Q. None of your studies include 4 cosmetic-grade talc or talc from any mine 5 that has been sourced from these two 6 products, correct? 7 MR. FROST: Objection to 8 form. 9 THE WITNESS: Again, I 10 worked with industrial talcs, one 11 a Barrett mining talc. I don't 12 know whether it's been sourced for 13 cosmetic talcs. 14 BY MR. SMITH: 15 Q. Well, you've never worked 16 with talc from Vermont, correct, 17 cosmetic-grade talc from Vermont? 18 A. That's correct. 19 Q. You've never worked with 20 cosmetic-grade talc from China, correct? 21 A. That's correct. 22 Q. You've never worked with 23 cosmetic-grade talc from Italy, correct? 24 A. Correct.</p>	<p>Page 180</p> <p>1 form. 2 THE WITNESS: None, to my 3 knowledge. 4 BY MR. SMITH: 5 Q. You've never seen the report 6 of Dr. Longo? 7 A. I'm aware he has one. I 8 have not reviewed it for this case. 9 Q. You didn't think it was 10 important to know what the testing 11 results were from the '60s, '70s, '80s, 12 '90s, and 2000s from Johnson &amp; Johnson 13 bottles from their own possession from 14 their own museum regarding the presence 15 of asbestos or not? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yeah, I had no 19 information suggesting that 20 asbestos was found in cosmetic 21 talcs. And I would assume that 22 Dr. Longo's information is 23 court-related and not in the 24 peer-reviewed scientific</p>
<p>Page 179</p> <p>1 Q. Okay. You've never 2 performed any animal inhalation studies 3 with Baby Powder or Shower to Shower, 4 correct? 5 A. That's correct. 6 Q. And you've never performed 7 any animal inhalation studies with 8 cosmetic-grade talc or talc from any mine 9 that has been sourced from these two 10 products, correct? 11 A. That's correct. 12 Q. You've never performed any 13 work or studies on Johnson &amp; Johnson's 14 Baby Powder or Shower to Shower, correct? 15 A. Correct. 16 Q. Do you know what the fiber 17 or mineral size of these two products 18 are? 19 A. I have not looked at fiber 20 size dimensions of cosmetic talcs, no. 21 Q. What types of asbestos have 22 been found in Johnson &amp; Johnson Baby 23 Powder and Shower to Shower? 24 MR. FROST: Objection to</p>	<p>Page 181</p> <p>1 literature. So for that reason, I 2 wouldn't have looked at it. 3 BY MR. SMITH: 4 Q. Well, the fact that you have 5 an opinion that cosmetic-grade talc, 6 which you've never done any studies on, 7 is not a risk factor or cause of ovarian 8 cancer, and those are your opinions in 9 this case as you stated earlier, don't 10 you think it would be pretty important to 11 know if there are any carcinogenic 12 substances that are found in the products 13 that are at issue in this case before 14 rendering that opinion? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Again, that's 18 why I read the IARC information, 19 and IARC in 2010 says that there 20 are no asbestos fibers in cosmetic 21 talcs. 22 BY MR. SMITH: 23 Q. Have you reviewed the 24 internal documents of Johnson &amp; Johnson</p>

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<p style="text-align: right;">Page 182</p> <p>1 and Imerys to see the numerous times that 2 different types of asbestos have been 3 found in their products, in their own 4 internal testing? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: No. I 8 wouldn't know what documents to 9 even ask for. 10 BY MR. SMITH: 11 Q. Don't you think it's 12 important -- again, if you're going to 13 render an opinion about -- and we're 14 talking about -- at issue in this case is 15 cosmetic-grade talc, not industrial, 16 right? 17 A. Correct. 18 Q. And we're talking about two 19 products, Baby Powder and Shower to 20 Shower, applied to a woman's genital area 21 and that causing ovarian cancer, correct? 22 A. Again, I emphasize that it 23 wouldn't make any difference whether 24 there was a small amount of asbestos in</p>	<p style="text-align: right;">Page 184</p> <p>1 A. That there is not a 2 significantly increased risk of ovarian 3 cancer that's related to dose dependency 4 of talc use in these studies. 5 Q. Let's -- let's get it 6 straight. 7 So the meta-analyses that 8 you looked at in forming the basis of 9 your opinion that talc does not cause or 10 is a risk factor for ovarian cancer, you 11 based in part on also the meta-analyses 12 for which you say those meta-analyses 13 state consistently the same thing, that 14 talc -- in those studies show that talc 15 does not cause -- those studies did not 16 show that talc increases the risk of 17 ovarian cancer and that -- that finding 18 is statistically significant, correct? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: We'd have to 22 go back to the papers. I'm aware 23 that the meta-analyses that I've 24 looked at may have been for the</p>
<p style="text-align: right;">Page 183</p> <p>1 there, in terms of my opinion. Those 2 talcs were used by individuals, I'm sure, 3 in the Women's Health Initiative, the 4 Gonzalez study and the Nurses' Health 5 study used cosmetic talcs, and they 6 didn't report an increase in ovarian 7 cancers. 8 So in attempting to go back 9 in time and point out discovery of a few 10 fibers is not conclusive evidence in any 11 regard in terms of my opinions. 12 Q. You did not look at any 13 meta-analyses in this case, did you? 14 A. Meta-analyses? I certainly 15 did. I looked at meta-analyses in terms 16 of the epidemiology. 17 Q. What did the meta-analyses 18 of talc and ovarian cancer risk reveal? 19 A. The meta-analyses with the 20 exception of, I believe it's 21 Penninkilampi who eliminated one of the 22 more recent cohort studies, all say the 23 same thing. 24 Q. What's that?</p>	<p style="text-align: right;">Page 185</p> <p>1 case-related studies or the 2 case-control studies. And with 3 the exception of Penninkilampi, 4 the meta-analyses that I looked at 5 did not suggest an increase in 6 ovarian cancer that was associated 7 with talc use. 8 BY MR. SMITH: 9 Q. Okay. You do not know if 10 there are EMPs in Baby Powder or Shower 11 to Shower, do you? 12 A. I don't. 13 Q. You don't know if there are 14 EMPs in cosmetic-grade talc, do you? 15 A. I don't. 16 Q. Do you know if scientists 17 have found EMPs in Baby Powder or Shower 18 to Shower? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: Yeah, I 22 haven't seen it in the 23 peer-reviewed scientific 24 literature.</p>

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<p style="text-align: right;">Page 186</p> <p>1 BY MR. SMITH: 2 Q. You can't tell me whether or 3 not there's asbestiform talc in Baby 4 Powder or Shower to Shower, correct? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: Again, it 8 hasn't been indicated as such 9 and -- or published in the 10 peer-reviewed scientific 11 literature. 12 BY MR. SMITH: 13 Q. And again, you have not 14 looked at the reports of Dr. Longo or 15 Rigler. 16 Have you seen the -- the 17 publication of Dr. Blount? 18 A. I have -- the -- is this a 19 publication of many years ago, 40 years 20 ago? 21 Q. It's in the 1990s. 22 A. I did look at that at one 23 point, yes. 24 Q. Okay. What did it -- what</p>	<p style="text-align: right;">Page 188</p> <p>1 Q. Would you have liked to have 2 known that or seen that when you were 3 reviewing the study? 4 MR. FROST: Objection to 5 form. 6 THE WITNESS: Well, my -- 7 probably not. Because I know that 8 talc and fiber identification and 9 the methods used have become 10 increasingly more significant in 11 terms of newer approaches. So I 12 wouldn't have been interested in 13 her work, which I believe was 40 14 or 50 years ago and had 15 questionable use of the 16 appropriate techniques. 17 BY MR. SMITH: 18 Q. Okay. You are aware that -- 19 you are not an expert in testing for 20 asbestos, are you, the presence of 21 asbestos? 22 A. I'm not. 23 Q. Did you understand that the 24 Blount method is a recognized method for</p>
<p style="text-align: right;">Page 187</p> <p>1 did it say? 2 A. It was confusing in terms of 3 her use of the nomenclature of talc, 4 which she referred to as sometimes 5 acicular, other types fibrous. It was 6 difficult to interpret that paper. 7 Q. So, you don't know whether 8 or not they talked about whether there 9 was asbestiform in -- found in Johnson &amp; 10 Johnson's Baby Powder or Shower to Shower 11 products? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah, I don't 15 recall that this paper identified 16 the products that she examined. 17 BY MR. SMITH: 18 Q. Okay. Have you ever seen 19 any other testimony or asked for any 20 other testimony or been shown any 21 testimony that reveals what the source of 22 her study was, that being talc? 23 A. I -- yeah, I don't recall. 24 Recently, no.</p>	<p style="text-align: right;">Page 189</p> <p>1 testing for asbestos in -- in certain 2 products? 3 MR. FROST: Objection to 4 form. 5 THE WITNESS: Again, I 6 emphasize that she used a 7 concentration method to 8 concentrate materials and I 9 believe that is accepted, but has 10 been questioned by scientists. 11 I am quite certain that she 12 didn't use other approaches such 13 as zonal access x-ray diffraction, 14 which is state of the art today, 15 for fiber identification. 16 BY MR. SMITH: 17 Q. Do you know if Dr. Longo and 18 Dr. Rigler did that on the products that 19 were provided them by Johnson &amp; Johnson? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: I don't know. 23 BY MR. SMITH: 24 Q. And again, you are not an</p>

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<p style="text-align: right;">Page 190</p> <p>1 expert in identifying asbestos in 2 materials, right? 3 A. I don't look at air samples 4 or lung digests for asbestos fibers. 5 Q. Or -- or evaluate, for 6 instance, Baby Powder or Shower to Shower 7 to determine whether asbestos, heavy 8 metal, silica, were present, correct? 9 A. I don't do that. I'm a 10 biologist. 11 Q. Do you know whether or not 12 there are carcinogenic heavy metals in 13 Baby Powder and Shower to Shower? 14 A. Again, the carcinogens that 15 had been listed by Dr. Selikoff in her 16 report have not given rise in 17 epidemiology or animal studies to ovarian 18 cancers. 19 Q. Do you know whether or not 20 there is carcinogenic crystalline silica 21 in Baby Powder or Shower to Shower? 22 A. I don't. 23 Q. We talked about the 24 different types of asbestos earlier. Do</p>	<p style="text-align: right;">Page 192</p> <p>1 document before, Doctor? 2 A. I have. 3 Q. And this is on asbestos, 4 chrysotile, amosite, crocidolite, 5 tremolite, actinolite, and anthophyllite, 6 and this is the IARC monograph, right? 7 A. Yes. 8 Q. And if you flip to Page 253, 9 it's Page 35 of 92 down at the bottom. 10 If you look at the very bottom of the 11 page, Doctor. It discusses cancer of the 12 ovary. 13 A. 35 of 92? 14 Q. Yes, ma'am. 15 A. Okay. 16 Q. Do you see that? 17 A. Yes. 18 Q. And then it goes on, on 19 Page 76 of 92, for the evaluation. It's 20 near the end. It states, "There is 21 sufficient evidence in humans for the 22 carcinogenicity of all forms of asbestos, 23 chrysotile, crocidolite, amosite, 24 tremolite, actinolite, and</p>
<p style="text-align: right;">Page 191</p> <p>1 you recall that? 2 A. I do. 3 Q. And we were -- I was asking 4 you whether or not you thought that all 5 types of asbestos were carcinogenic to 6 humans. Do you recall that? 7 A. I do. 8 Q. And we discussed the NTP and 9 IARC have determined that all forms of 10 asbestos are known human carcinogens, 11 correct? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: That is stated 15 in terms of their regulatory 16 policies, yes. 17 BY MR. SMITH: 18 Q. I will attach, the next 19 numbered exhibit is 19. 20 (Document marked for 21 identification as Exhibit 22 Mossman-19.) 23 BY MR. SMITH: 24 Q. And you've seen this</p>	<p style="text-align: right;">Page 193</p> <p>1 anthophyllite." 2 A. Could you point -- 3 MR. FROST: I was going to 4 say, where are you reading from? 5 THE WITNESS: Yeah. 6 MR. SMITH: I'm sorry. I 7 might not have said it. I might 8 have been thinking it and didn't 9 say it. 10 BY MR. SMITH: 11 Q. Page 76 of 92, down at the 12 bottom -- 13 MR. FROST: Oh, under 14 evaluation? 15 MR. SMITH: Yeah, under 16 evaluation. 17 THE WITNESS: 76. 18 MR. SMITH: It's under 19 evaluation. 20 THE WITNESS: Okay. 21 MR. FROST: Now we are on 22 the same page. 23 BY MR. SMITH: 24 Q. All right. And it says,</p>

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<p style="text-align: right;">Page 194</p> <p>1 "There is sufficient evidence of" -- "in 2 humans for the carcinogenicity of all 3 forms of asbestos. Asbestos causes 4 mesothelioma and cancer of the lung, 5 larynx, and ovary." 6 Do you see that? 7 A. Yes. 8 Q. And that's what we were 9 talking about earlier when I was talking 10 about IARC? 11 A. Yes. 12 Q. And then it says at the 13 bottom, "All forms of asbestos, 14 chrysotile, crocidolite, amosite, 15 tremolite, actinolite, and anthophyllite, 16 are carcinogenic to humans Group 1." 17 Do you see that? 18 A. I do. 19 Q. Is that what we were 20 discussing earlier? 21 A. Yes. 22 Q. We talked about earlier that 23 talc with asbestiform fibers is also a 24 known human carcinogen as well by IARC;</p>	<p style="text-align: right;">Page 196</p> <p>1 bulletin, right, of Bulletin 62 of NIOSH? 2 A. I did. 3 Q. And you weren't aware that 4 Dr. -- that Dr. Michaels served on that 5 as well, with you? You weren't aware of 6 that, right? 7 A. He wasn't on the committee 8 meetings that I attended. So I'm not 9 sure what -- where he was. He may have 10 been someone that -- okay, he may have 11 been someone that served in some 12 capacity. I just don't recall it. 13 (Document marked for 14 identification as Exhibit 15 Mossman-20.) 16 BY MR. SMITH: 17 Q. I'm going to attach as 18 Exhibit 20. This is current intelligence 19 Bulletin 62, "Asbestos fibers and other 20 elongated mineral particles, state of the 21 science and roadmap for research." 22 And this was put out by the 23 Department of Health and Human Services 24 and NIOSH, correct?</p>
<p style="text-align: right;">Page 195</p> <p>1 is that correct? 2 A. They classify it as such. 3 Q. And we went through also the 4 Prop 65 listing. Do you recall that for 5 asbestiform talc? 6 A. Yes. I'm not sure what that 7 said exactly, but I don't think we 8 discussed that. 9 Q. Well, let's discuss it. It 10 says, "Talc containing asbestiform 11 fibers." It's Exhibit 15. 12 It says, "Chemical listing 13 details." And it says, "Listed as 14 causing," and it says "cancer." 15 Do you see that? And date 16 of listing was on 4/1/1990? 17 A. Yes. 18 Q. Okay. And do you remember 19 us talking earlier, I asked you about if 20 you knew David Michaels, if he was -- and 21 we went through his book, his chapter in 22 the book on Regulatory Toxicology and 23 Pharmacology. And I asked you, you 24 served as a peer reviewer of this</p>	<p style="text-align: right;">Page 197</p> <p>1 A. Yes. 2 Q. And NIOSH is the scientific 3 arm of OSHA; is that correct? 4 A. Yes, it is. 5 Q. Responsible for health and 6 safety of American workers; is that 7 correct? 8 A. That's OSHA. NIOSH is more 9 a research body. 10 Q. And if you look at XVII. 11 It's in the front page. I guess that 12 would be 17. 13 A. Okay. 14 Q. It says -- do you see 15 "acknowledgments" at the top? Down at 16 the bottom right corner, Doctor? 17 A. Yes. 18 Q. XVII. It says peer 19 reviewers. Do you see that? 20 It says, "NIOSH greatly 21 appreciates the time and efforts of 22 expert peer reviewers who provided 23 comments and suggestions on the initial 24 publicly disseminated draft of the</p>



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<p>1 roadmap February 7, 2007, version." 2 Do you see that? 3 A. Yes, I do. 4 Q. And do you see David 5 Michaels, Ph.D. MPH, George Washington 6 University listed on that page? 7 A. I do. 8 Q. And then on the next page 9 you are listed on the top, correct? 10 A. Mm-hmm. 11 Q. Okay. If we go to -- let's 12 see. If you look at Page 33, Doctor. If 13 you look at the bottom right in the 14 footnote, if you go two, four, six -- six 15 lines down. It says, "The National 16 Toxicology Program, NTP, 2005, of which 17 NIOSH is a member, has determined that 18 asbestos in all commercial forms of 19 asbestos are known to be human 20 carcinogens based on sufficient evidence 21 of carcinogenicity in humans." 22 Do you see that? 23 MR. FROST: Want me to help 24 you?</p>	<p>1 internally by Johnson &amp; Johnson, Imerys 2 internally, or by Dr. Longo? 3 A. I don't. 4 Q. If I told you they were 5 tremolite, anthophyllite, and actinolite, 6 the majority of what was found, the vast 7 majority, you wouldn't have any basis or 8 any knowledge regarding that, right? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: Yeah, could 12 you repeat that again. 13 BY MR. SMITH: 14 Q. Tremolite, anthophyllite, 15 and actinolite. 16 A. And the -- 17 MR. FROST: Objection to 18 form. 19 THE WITNESS: Are you -- 20 yeah, are you saying that the 21 asbestos varieties of these have 22 been found in Baby Powder? 23 BY MR. SMITH: 24 Q. Yes, ma'am.</p>
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<p>1 THE WITNESS: Yeah, that 2 would be great. 3 MR. FROST: Do you mind if I 4 point to where you were? 5 MR. SMITH: Oh, yeah. No, 6 no, no. 7 THE WITNESS: I'm just -- 8 I'm looking at this. Okay. 9 BY MR. SMITH: 10 Q. Do you see that, Doctor, in 11 the footnote? 12 A. Yes. 13 Q. Okay. 14 (Whereupon, a discussion was 15 held off the stenographic record.) 16 BY MR. SMITH: 17 Q. All right, Doctor, different 18 types of asbestos vary in potency as 19 carcinogens; however, they're all 20 recognized as carcinogens, right? 21 A. Yes. In animals, yes. 22 Q. And I asked you this 23 earlier. Do you know the types of 24 asbestos that were found either</p>	<p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: Okay. 4 BY MR. SMITH: 5 Q. And you haven't seen the 6 internal documents of Johnson &amp; Johnson 7 regarding this matter, have you? 8 A. I haven't. 9 Q. And you haven't seen the 10 internal documents of Imerys or Luzenac, 11 have you, on this? 12 A. That's correct. 13 Q. And you have not seen the 14 reports of Dr. Longo and Rigler, correct? 15 A. Correct. 16 MR. SMITH: What is the 17 geologist's name? 18 BY MR. SMITH: 19 Q. And you haven't seen the 20 geologist expert Cook, Dr. Cook in this 21 case, you haven't seen his report, have 22 you? 23 A. I might have scanned his 24 report, but I don't recall it</p>

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<p style="text-align: right;">Page 202</p> <p>1 specifically.</p> <p>2 Q. Okay. Have you -- we'll get</p> <p>3 back to that in a minute.</p> <p>4 Your personal research has</p> <p>5 not dealt with tremolite asbestos,</p> <p>6 correct?</p> <p>7 A. No. I've only looked at</p> <p>8 tremolite in its non-asbestos form.</p> <p>9 Q. Your personal research has</p> <p>10 not dealt with tremolite asbestos,</p> <p>11 correct?</p> <p>12 MR. FROST: Objection to</p> <p>13 form.</p> <p>14 THE WITNESS: Yeah. I've</p> <p>15 looked at tremolite, but not the</p> <p>16 asbestos. That's correct.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Your personal research has</p> <p>19 not dealt with anthophyllite asbestos,</p> <p>20 correct?</p> <p>21 A. I have not used</p> <p>22 anthophyllite, that's correct.</p> <p>23 Q. Your personal research has</p> <p>24 not dealt with actinolite asbestos,</p>	<p style="text-align: right;">Page 204</p> <p>1 Q. Yours did too?</p> <p>2 A. Yeah.</p> <p>3 Q. Wasn't a very good job of</p> <p>4 binding that, was it?</p> <p>5 Bear with me just a second.</p> <p>6 And to your knowledge there are no</p> <p>7 detailed studies comparing the chemistry</p> <p>8 of tremolite asbestos to tremolite</p> <p>9 cleavage fragments, correct?</p> <p>10 A. That would be a question</p> <p>11 that should be posed to a geologist. I</p> <p>12 have not looked at the mineralogy</p> <p>13 literature for those comparisons.</p> <p>14 Q. With regard to anthophyllite</p> <p>15 asbestos and anthophyllite cleavage</p> <p>16 fragments, you have not studied the</p> <p>17 differences in chemistry between the two,</p> <p>18 correct?</p> <p>19 A. That's correct.</p> <p>20 Q. And the same with regard to</p> <p>21 actinolite asbestos and actinolite --</p> <p>22 actinolite cleavage fragments?</p> <p>23 A. That's correct.</p> <p>24 Q. And aside from the one study</p>
<p style="text-align: right;">Page 203</p> <p>1 correct?</p> <p>2 A. That's correct.</p> <p>3 Q. You cannot tell me how</p> <p>4 carcinogenic or potent tremolite or</p> <p>5 anthophyllite are, correct?</p> <p>6 MR. FROST: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: Again, I can</p> <p>9 tell you based on the epidemiology</p> <p>10 that anthophyllite is a weak agent</p> <p>11 in the development of</p> <p>12 mesotheliomas as compared to</p> <p>13 crocidolite or amosite asbestos.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You have never studied the</p> <p>16 differences between tremolite asbestos</p> <p>17 and tremolite cleavage fragments,</p> <p>18 correct?</p> <p>19 A. I haven't used the two</p> <p>20 comparatively in experiments, that's</p> <p>21 correct.</p> <p>22 Q. This thing fell apart.</p> <p>23 That's crazy.</p> <p>24 A. Mine fell apart too.</p>	<p style="text-align: right;">Page 205</p> <p>1 in upstate New York on talc, you've never</p> <p>2 studied tremolite or anthophyllite</p> <p>3 cleavage fragments yourself, correct?</p> <p>4 A. The study that I performed</p> <p>5 was with Dr. Wiley.</p> <p>6 Q. Aside from the one study in</p> <p>7 upstate New York on talc, you have never</p> <p>8 studied tremolite or anthophyllite</p> <p>9 cleavage fragments yourself, have you?</p> <p>10 MR. FROST: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Correct. It's</p> <p>13 just that one study.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. And the talc in your New</p> <p>16 York study that we just discussed was</p> <p>17 a -- an industrial grade talc and not</p> <p>18 cosmetic-grade talc; is that correct?</p> <p>19 A. Yes. There were three</p> <p>20 samples of talc with various proportions</p> <p>21 of fibers.</p> <p>22 Q. You have not studied how</p> <p>23 tremolite, anthophyllite, and actinolite</p> <p>24 asbestos reached the areas of the lungs</p>

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<p>Page 206</p> <p>1 where meso is induced and developed, and 2 you cannot make a strict analogy to these 3 types of asbestos from your study of 4 other types of asbestos; is that correct? 5 MR. FROST: Objection to 6 form. 7 THE WITNESS: Yeah, I -- I'd 8 have to ask someone who is an 9 expert in dosimetry. Assuming 10 that dimensions of fibers govern 11 where they end up in the lung, the 12 results that we have may be 13 relevant certainly to these types 14 of materials. 15 BY MR. SMITH: 16 Q. Okay. I'm going to ask the 17 question again. I don't think it was 18 responsive. 19 You have studied -- you have 20 not studied how tremolite, anthophyllite, 21 and actinolite asbestos reached the area 22 in the lungs where meso is induced and 23 developed, correct? 24 MR. FROST: Objection to</p>	<p>Page 208</p> <p>1 In the -- it's broken up. 2 Whatever. 3 MR. FROST: Mine stayed 4 together. 5 THE WITNESS: Yeah, mine is 6 broken, so... 7 MR. FROST: 179 you said? 8 MR. SMITH: Yes, please. 9 MR. FROST: Here, do you 10 want -- do you want to switch, 11 Brooke? 12 THE WITNESS: That's okay. 13 MR. FROST: Mine is still 14 bound. So do you want to switch? 15 THE WITNESS: I think I'm 16 prime viewing here. 17 No, just in different 18 pieces. 179. 19 Okay. 20 BY MR. SMITH: 21 Q. All right. On Line 11: 22 "And then you were asked the following 23 question: 24 "Okay. Well, I think the</p>
<p>Page 207</p> <p>1 form. 2 THE WITNESS: I -- yeah, I 3 have not studied those three 4 materials in inhalation 5 experiments. 6 BY MR. SMITH: 7 Q. And you cannot make a strict 8 analogy as to these types of asbestos 9 from your other study -- from your study 10 of other types of asbestos; is that 11 correct? 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: And -- and my 15 comment was that if they are of 16 the same dimensional 17 characteristics of the materials 18 that I use, namely crocidolite 19 asbestos, I could make some 20 analogies based upon their size 21 and fiber characteristics. 22 BY MR. SMITH: 23 Q. Okay. The -- I want you to 24 go to Page 179 in Leavitt, please.</p>	<p>Page 209</p> <p>1 record will speak for itself, but I think 2 you did give that in your answer when I 3 asked you. Let me ask you generally. 4 "This whole set of opinions 5 regarding how minerals such as asbestos 6 get to sites where mesothelioma is 7 induced and developed, does that apply to 8 tremolite, actinolite, and 9 anthophyllite?" 10 "And your answer: I don't 11 know. These, again, the animal studies 12 have been done with short and long 13 amosite asbestos and they have been done 14 with crocidolite asbestos. And the 15 groups that have done these experiments 16 have not looked at tremolite and 17 actinolite or anthophyllite because they 18 are the least potent types of asbestos. 19 So I can't make a strict analogy between 20 what's been studied and the asbestos 21 types that I" -- "that haven't been 22 studied." 23 "Did I read that correctly? 24 "And your answer was that's</p>

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<p style="text-align: right;">Page 210</p> <p>1 correct."</p> <p>2 Can I rely on that</p> <p>3 testimony?</p> <p>4 A. You -- you can.</p> <p>5 Q. Okay. You have not studied</p> <p>6 the bio durability of asbestos cleavage</p> <p>7 fragments or talc in any human tissue,</p> <p>8 correct?</p> <p>9 A. I have not looked at tissue</p> <p>10 digestion studies, that's correct.</p> <p>11 Q. You have not performed any</p> <p>12 studies on whether cleavage fragments can</p> <p>13 reach the area of the lung where meso</p> <p>14 is -- mesothelioma is induced and</p> <p>15 develops, correct?</p> <p>16 A. I have not done inhalation</p> <p>17 studies with cleavage fragments.</p> <p>18 Q. And you have not performed</p> <p>19 any studies on whether cleavage fragments</p> <p>20 can reach the area of the lung -- excuse</p> <p>21 me, reach the area -- excuse me. Let me</p> <p>22 back up. I'm going to get it right here</p> <p>23 in a second.</p> <p>24 You have not performed any</p>	<p style="text-align: right;">Page 212</p> <p>1 cleavage fragment as opposed to the</p> <p>2 asbestos fiber is beyond the scope of</p> <p>3 your expertise, correct?"</p> <p>4 And your answer under</p> <p>5 that -- under oath at that time was, "I</p> <p>6 do not do the measurements, no.</p> <p>7 That's" -- "that's correct."</p> <p>8 Is that true?</p> <p>9 A. No, actually, I have done</p> <p>10 the measurements with Dr. Woodworth on</p> <p>11 preparations of cleavage fragments and</p> <p>12 the respective asbestos fiber</p> <p>13 preparations, and that was done in the</p> <p>14 1980s and '90s.</p> <p>15 Q. So this was just a</p> <p>16 misstatement in Leavitt?</p> <p>17 MR. FROST: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: Yeah, I don't</p> <p>20 think it was a misstatement. I --</p> <p>21 I say, "I don't do the</p> <p>22 measurements in each experiment.</p> <p>23 I have in the past."</p> <p>24 So that's what I was</p>
<p style="text-align: right;">Page 211</p> <p>1 studies on whether talc can reach the</p> <p>2 area of the ovaries which can lead to</p> <p>3 ovarian cancer, correct?</p> <p>4 A. I have not studied migration</p> <p>5 of talc.</p> <p>6 Q. Distinguishing the</p> <p>7 dimensions, the aspect ratio of a</p> <p>8 cleavage fragment as opposed to an</p> <p>9 asbestos fiber is beyond the scope of</p> <p>10 your expertise, correct?</p> <p>11 A. I have done some work on</p> <p>12 dimensional characteristics in the 1980s,</p> <p>13 where we compared cleavage fragment</p> <p>14 population to asbestos fibers and those</p> <p>15 are papers by Woodworth, et al., and</p> <p>16 Hansen, et al., in cancer research.</p> <p>17 Q. Okay. Can you go to 193 of</p> <p>18 the Leavitt testimony, please?</p> <p>19 A. Okay.</p> <p>20 Q. And it's down on page -- I</p> <p>21 mean, excuse me, Line 23.</p> <p>22 "Question" -- and you were</p> <p>23 asked, "Simply put, distinguishing the</p> <p>24 dimensions, the aspect ratio of the</p>	<p style="text-align: right;">Page 213</p> <p>1 referring to. That's in the next</p> <p>2 six to eight lines on 194.</p> <p>3 BY MR. SMITH:</p> <p>4 Q. And then you continue on by,</p> <p>5 "Now I give it to a -- someone in our</p> <p>6 cell imaging facility," correct?</p> <p>7 A. Right. We have people who</p> <p>8 do those measurements.</p> <p>9 Q. Okay. You've never measured</p> <p>10 the flexibility or tensile strength of</p> <p>11 asbestos or cleavage fragments, correct?</p> <p>12 A. That's correct. I don't</p> <p>13 measure flexibility.</p> <p>14 Q. Flexibility of asbestos</p> <p>15 fiber within a lung cell causing</p> <p>16 mechanical injury is just a hypothesis,</p> <p>17 correct?</p> <p>18 A. Well -- well, it --</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: Yeah, it was</p> <p>22 originally hypothesized by someone</p> <p>23 named Archer who looked at plastic</p> <p>24 films and measured the amount of</p>

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<p>1 free radical generation and 2 flexibility. So I think it's more 3 than a hypothesis. It's been 4 proven by some experimental data. 5 BY MR. SMITH: 6 Q. Go to Page 172 in your 7 Leavitt testimony. 8 A. Okay. 9 Q. And I'm -- I'm going to 10 hopefully maybe get you a better copy or 11 something. 12 A. It's okay. We're getting 13 there. 14 Q. All right. 172. Line 15. 15 "Okay. When" -- "when asked 16 about flexibility you said in the past 17 there is a hypothesis that the 18 flexibility of an asbestos fiber within 19 the lung within a cell can cause 20 mechanical injury, correct? 21 "Yeah" -- and your answer 22 was, "Yes." 23 "Question: Okay. But 24 that's a hypothesis, correct?"</p>	<p>1 THE WITNESS: Want to take a 2 short -- 3 MR. FROST: Yeah, so why 4 don't we take like a five-minute 5 break and then -- I mean, I'm 6 generally fine going through 7 lunch. I don't normally take 8 lunches, but if the witness if 9 fine and you're fine -- 10 MS. O'DELL: What's your 11 preference though? 12 THE WITNESS: It -- it's up 13 to you. I'd just as soon go. 14 MR. SMITH: Well, we're 15 going to have a -- 16 MS. O'DELL: I think we 17 should have lunch at some point. 18 MR. SMITH: I'm going to 19 have to eat something. 20 THE WITNESS: Okay. 21 MR. FROST: Okay. How long 22 is your next section? Is it like 23 half an hour, 45 minutes? 24 MR. SMITH: That's a good</p>
Page 215	Page 217
<p>1 And your answer was what? 2 A. My answer was, "Yes." But 3 as I just stated, there have been studies 4 showing that flexibility within a cell 5 can cause oxidants that then are 6 associated with a mechanical injury. 7 So this statement is -- is 8 correct, but I think my statement in 9 terms of Archer experiments, it -- also 10 relate to flexibility and things that 11 injure cells. 12 Q. Is your -- can I rely on 13 your answer in Leavitt right there? 14 A. Sure. 15 MR. SMITH: Okay. I'm 16 getting ready to move to a 17 different section. Are we 18 breaking for lunch, are we just 19 going to plow through? What do 20 you want to do? 21 THE WITNESS: Let's go 22 through. 23 MR. FROST: Yeah, I was 24 going to say --</p>	<p>1 question. I think we probably 2 better break now. 3 MR. FROST: You want to 4 break now? 5 MR. SMITH: Yeah. 6 THE WITNESS: Okay. 7 MR. SMITH: Is that okay? 8 THE WITNESS: Sure. 9 MR. FROST: Yeah, that's 10 fine. 11 THE VIDEOGRAPHER: Going off 12 record. The time is 12:16. 13 - - - 14 (Lunch break.) 15 - - - 16 A F T E R N O O N S E S S I O N 17 - - - 18 THE VIDEOGRAPHER: We are 19 going back on record beginning 20 Media File Number 3. The time is 21 1:22. 22 - - - 23 EXAMINATION (Cont'd.) 24 - - -</p>

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<p style="text-align: right;">Page 218</p> <p>1 BY MR. SMITH: 2 Q. All right. Doctor, we just 3 took a lunch break, and I just have some 4 more questioning for you. 5 In your paper -- excuse me, 6 in your report for the MDL, you state, on 7 Page 10, under Paragraph D, "Chronic 8 inflammation and foreign body 9 carcinogenesis." And I quote, "Chronic 10 inflammation over months and years can 11 result in many diseases, including 12 cancers, but has not been established as 13 a cause of ovarian cancer, and there is 14 evidence that is difficult to reconcile 15 with the inflammation hypothesis." And 16 you have Ni cited. 17 And then you go on to say, 18 "The relationship between cancer and 19 inflammation is not simple and cannot be 20 reduced to one grand theory," quoting 21 Rakoff-Nahoum, 2006. Do you recall that 22 in your report? 23 A. Yes. Do you -- 24 MR. FROST: So yeah, I was</p>	<p style="text-align: right;">Page 220</p> <p>1 "Chronic inflammation and foreign body 2 carcinogenesis." 3 A. Yes. 4 Q. Did I read that correctly? 5 It's the -- it's six lines down starting 6 with, "Chronic inflammation," to the 7 right. I'll read it again. 8 A. Yes. 9 Q. "Chronic inflammation over 10 months and years can result in many 11 diseases including cancers but has not 12 been established as a cause of ovarian 13 cancer, and there is evidence that is 14 difficult to reconcile with the 15 inflammation hypothesis." You cite Ni, 16 et al., 2012. 17 "Notably Rakoff-Nahoum, 18 2006, cautions, 'The relationship between 19 cancer and inflammation is not simple and 20 cannot be reduced to one grand theory.'" 21 Did I read that correctly? 22 A. You did. 23 Q. Okay. And this is in your 24 MDL report as part of your opinion in</p>
<p style="text-align: right;">Page 219</p> <p>1 going to say, can we mark a copy 2 of the report? It might make it 3 easier. 4 MR. SMITH: Sure. I have 5 some copies. 6 (Document marked for 7 identification as Exhibit 8 Mossman-21.) 9 BY MR. SMITH: 10 Q. I'm going to mark a clean 11 copy. 12 MR. SMITH: Can I keep one 13 of them? 14 MR. FROST: Sure. I was 15 going to say, is one marked up? 16 MR. SMITH: Yeah. 17 BY MR. SMITH: 18 Q. And that would be the next 19 numbered exhibit, Exhibit 21. And, 20 Doctor, I was reading on Page 10 of your 21 report. 22 A. Okay. 23 Q. From Page 10 of your report. 24 Right in that first paragraph under,</p>	<p style="text-align: right;">Page 221</p> <p>1 this case, correct? 2 A. It is. 3 MR. SMITH: I'm going to try 4 to make this as easy as possible. 5 But I put together -- it's a 6 two-sided document. 7 I'm going to mark it as the 8 next exhibit. It's going to be 9 12. And I created this. 10 MR. FROST: Object for the 11 record the use to compiled, 12 created. This is two pages? We 13 only have one. 14 But to finish my objection, 15 but yeah, I object to the use of, 16 you know, exhibits that you 17 created. 18 MR. SMITH: There should be 19 a back and front. 20 MR. FROST: That's what I 21 figured. Yeah, it's just the -- 22 THE WITNESS: It's just Page 23 1. 24 MR. SMITH: All right.</p>

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<p style="text-align: right;">Page 222</p> <p>1 Well, let's do this. I'm going to 2 mark -- and we'll go through it. 3 I'm going to have to probably do 4 it back on the Elmo because I 5 don't know what happened. They 6 copied this downstairs. I 7 don't -- I don't have an 8 explanation. 9 I'm going to mark, which is 10 the back and front, which you just 11 have the front, as Exhibit 24. 12 And then when we get to the back 13 of it, I'm going to have to use 14 the Elmo. 15 (Document marked for 16 identification as Exhibit 17 Mossman-24.) 18 BY MR. SMITH: 19 Q. I just want to go through 20 these studies. And just walk through 21 them with you and ask you some questions. 22 They're quotes from these different 23 studies. And first let me ask you. 24 Let's go to the first one.</p>	<p style="text-align: right;">Page 224</p> <p>1 No. I actually scanned it because 2 it was presented to me in another 3 matter while on the stand. So I 4 did not look at it in detail. 5 BY MR. SMITH: 6 Q. Okay. So you've not read 7 this back to front, this draft screening 8 assessment from Health Canada? 9 A. That's -- that's correct. 10 Q. You were just asked 11 questions about certain parts of it on 12 the stand, witness stand? 13 A. I was. 14 Q. Okay. Was that in the 15 Leavitt case? 16 A. I believe so, yes. 17 Q. Second quote from this draft 18 screening assessment on this page: 19 "There is support for an association of 20 inflammation and increased risk of 21 ovarian cancer." 22 Would you agree or disagree 23 with that statement? 24 MR. FROST: Objection to</p>
<p style="text-align: right;">Page 223</p> <p>1 The draft screening 2 assessment "Talc, Environment, and 3 Climate Change," Canada, Health Canada 4 December 2018. Did you use that as part 5 of your reliance materials for your 6 opinion in this case? 7 A. I did not. 8 Q. Okay. And it says, "With 9 respect to talc specifically, local 10 irritation leading to an inflammatory 11 response is one of the possible 12 mechanisms of tumor progression that is 13 frequently hypothesized." 14 You've not read the Health 15 Canada draft screening assessment 16 referenced here? 17 A. I have scanned it, yes. 18 Q. You just said you hadn't 19 seen it. Now you say you scanned it. 20 Which is it? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: You asked me 24 if I read it in its completeness.</p>	<p style="text-align: right;">Page 225</p> <p>1 form. 2 THE WITNESS: I would 3 disagree with both of them. 4 Although I think the first one 5 states possible and hypothesis. 6 And again local irritation is a 7 hypothesis. But I would disagree 8 with both of them. 9 BY MR. SMITH: 10 Q. And the -- the second -- the 11 third paragraph down cites the second 12 article -- a second article, Taher. Have 13 you read Taher in reliance of your 14 opinions in this case? 15 A. No, I see this is an 16 unpublished document. 17 Q. Well, it is an unpublished 18 document that's been published. It's in 19 peer-reviewed literature. 20 Taher, you've never read it? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: Yeah. I am 24 unaware of it. And if it has been</p>

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<p style="text-align: right;">Page 226</p> <p>1 published in the peer-review 2 literature, it hasn't appeared on 3 my searches. 4 MR. SMITH: And that is -- 5 I'm going to mark this as 6 Exhibit 22. 7 Is that correct? 8 (Document marked for 9 identification as Exhibit 10 Mossman-22.) 11 MS. O'DELL: This is 24. 12 MR. SMITH: Oh my gosh. 13 MS. O'DELL: We didn't do a 14 20 -- 15 MR. FROST: Oh, I see. 16 Okay. 17 MR. SMITH: Does it really 18 matter? 19 MR. FROST: I was going to 20 say we can do 22. I don't think 21 it has been -- 22 MR. MIZGALA: So this, this 23 is 24? 24 MR. SMITH: Yeah, this is</p>	<p style="text-align: right;">Page 228</p> <p>1 inflammation in local immunogenicity has 2 been linked to causation of ovarian 3 cancers in anything that I've read. 4 Q. But you haven't read Taher? 5 A. No. This is an unpublished 6 document. I'm not sure where it's 7 published. 8 I haven't seen this document 9 and certainly I never saw it before my 10 report. So I would wonder what's new 11 about it and what's the source. I don't 12 know of any of the authors and haven't 13 heard of them as well. So I couldn't 14 really comment on this. 15 Q. You don't know -- have any 16 knowledge about whether this 17 meta-analysis was produced and submitted 18 to Health Canada for their risk 19 assessment of talc not containing 20 asbestos? 21 A. No, it -- 22 MR. FROST: Objection to 23 form. 24 BY MR. SMITH:</p>
<p style="text-align: right;">Page 227</p> <p>1 24 -- 2 MR. FROST: So I think this 3 one will be 22. 4 MR. SMITH: It doesn't 5 matter what number. 6 MR. FROST: We can use 22 7 and 23 now. 8 MR. SMITH: Yeah. Okay. 9 BY MR. SMITH: 10 Q. This is a systematic review 11 of the meta-analysis of the association 12 between perineal use of talc and risk of 13 ovarian cancer. Have you read and relied 14 on this study in support of your opinion 15 in this case? 16 A. I have not seen this study 17 before. 18 Q. Okay. And the quote on 19 Page 26, "Chronic inflammatory response 20 and alteration in local immunogenicity 21 are possible mechanisms." 22 Would you agree with that, 23 as far as mechanisms for ovarian cancer? 24 A. I don't think that chronic</p>	<p style="text-align: right;">Page 229</p> <p>1 Q. Okay. 2 A. It's not in the 3 peer-reviewed literature. And I'm 4 unfamiliar with Dr. Taher or any of the 5 other authors in terms of their 6 contributions to the field. 7 Q. Next is a -- a study called 8 Penninkilampi 2018. You referenced that 9 earlier. 10 Did you rely on the 11 Penninkilampi study for the basis of any 12 of your opinions in this case? 13 A. Yes. But I emphasize that 14 this was a meta-analysis and a -- an 15 epidemiological study that didn't look 16 as -- at the quote as any foreign bodies. 17 And so I wouldn't agree with this 18 statement. 19 I don't think that there is 20 any information in this article or in 21 other ones that talc would ascend 22 perineally to the ovary. 23 Q. Quote, if chronic -- and I'm 24 quoting Penninkilampi. If chronic</p>

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<p style="text-align: right;">Page 230</p> <p>1 inflammation due to ascending foreign 2 bodies is indeed the mechanism by which 3 talc is associated with increased ovarian 4 cancer, then these revoked results fit 5 the picture. And you said that you don't 6 believe that talc can ascend through the 7 fallopian tubes to the ovaries; is that 8 correct? 9 A. And I'm -- 10 Q. And we'll get to that in a 11 minute about migration. 12 MR. FROST: Objection to 13 form. 14 THE WITNESS: Yeah, I think 15 that this -- the question if is 16 indeed the mechanism is unproven. 17 And certainly not in the 18 Penninkilampi epidemiological 19 meta-analysis. 20 BY MR. SMITH: 21 Q. Have you read the Trabert, 22 Pinto and Hartge, et al., 2014 document 23 and used that as a basis of your opinions 24 in this case?</p>	<p style="text-align: right;">Page 232</p> <p>1 But as I remember this statement, 2 it was referenced to a hypothesis 3 paper by Ness and -- I believe it 4 was Cottréau in 1999 or 2000. And 5 that was the reference for this 6 statement. Certainly not the 7 paper which I believe was looking 8 at systemic markers of 9 inflammation and not ovarian 10 related markers in the ovary. 11 BY MR. SMITH: 12 Q. There's another quote from 13 the Trabert study. "Our studies provide 14 additional evidence that inflammation 15 plays an important role in ovarian 16 carcinogenesis." 17 Would you agree or disagree 18 with that statement from Trabert? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: Again, I don't 22 have the paper in front of me, but 23 Trabert did not look at localized 24 inflammation in the ovary. I</p>
<p style="text-align: right;">Page 231</p> <p>1 A. I have. 2 Q. And quote from that study, 3 "Epidemiologic evidence implicates 4 chronic inflammation as a central 5 mechanism in the pathogenesis of ovarian 6 cancer." 7 What's pathogenesis means? 8 A. Pathogenesis means the 9 development of disease. So it could be 10 any -- it could be talking about anything 11 from causation to later stages of 12 disease. 13 Q. Well, here, "Epidemiologic 14 evidence implicates chronic inflammation 15 as a central mechanism in the 16 pathogenesis of ovarian cancer, the most 17 lethal gynecologic cancer among women in 18 the United States." 19 Would you agree or disagree 20 with that statement from Trabert? 21 MR. FROST: Objection to 22 form. 23 THE WITNESS: Yeah, I would 24 have to look at the Trabert paper.</p>	<p style="text-align: right;">Page 233</p> <p>1 believe this was a study where 2 they looked at a total of over 40 3 markers of inflammation and found 4 only two systemically in 5 individuals with preexisting 6 cancer. 7 So, if it does play a role 8 in ovarian carcinogenesis, it 9 certainly is very speculative with 10 regard to causation. 11 BY MR. SMITH: 12 Q. Well, it doesn't seem 13 speculative here. The quote states: 14 "Our study provides additional 15 evidence" -- "provides additional 16 evidence that inflammation plays an 17 important role in ovarian 18 carcinogenesis." 19 It's pretty direct there. 20 It doesn't say anything about hypothesis 21 or -- or any of the qualifiers that 22 you're saying, Doctor, does it? 23 MR. FROST: Objection to 24 form.</p>

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<p style="text-align: right;">Page 234</p> <p>1 THE WITNESS: Yeah, let me 2 emphasize though, here they are 3 looking at systemic markers of 4 inflammation in the serum of 5 patients, and some of the markers 6 they found are the same ones that 7 have been detected in lung cancers 8 or in other models of cancer. 9 So whether inflammation 10 plays a critical role is 11 speculative. 12 BY MR. SMITH: 13 Q. They didn't say it was 14 speculative? 15 MR. FROST: Objection to 16 form. 17 BY MR. SMITH: 18 Q. Correct? 19 A. They did not look at 20 inflammation in the ovary. So you can't 21 equate systemic inflammatory markers with 22 causative roles in disease especially if 23 you're looking at individuals who had 24 disease.</p>	<p style="text-align: right;">Page 236</p> <p>1 Would you agree or disagree 2 with that statement? 3 MR. FROST: Objection to 4 form. 5 THE WITNESS: I would 6 disagree that his studies 7 illustrated that endometriosis is 8 linked to the risk of ovarian 9 cancer. Other studies have shown 10 that it's not. 11 BY MR. SMITH: 12 Q. Have you relied on Merritt 13 2008 as a basis for your opinions in this 14 case? 15 A. Again, I'd have to go back 16 and -- did I list this in my references? 17 Then I could tell you. 18 Q. Well, let's look. 19 THE WITNESS: Do we have the 20 references? 21 MR. FROST: The references 22 aren't attached. 23 THE WITNESS: Yeah. 24 MR. SMITH: Hold on. I</p>
<p style="text-align: right;">Page 235</p> <p>1 MR. FROST: And she said it 2 in her answer. I was trying to 3 get it in before. I want to lodge 4 the general objection that I think 5 it's improper to be asking her 6 about questions about papers that 7 aren't in front of her. 8 BY MR. SMITH: 9 Q. Did you look at the Wu 2009 10 paper? 11 A. I did, and again, this is an 12 epidemiology paper. I'd have to look at 13 it again to see where the source of this 14 statement comes from, whether it's 15 reference to another study or whether 16 he's talking about specific things here 17 such as talc and endometriosis that he's 18 identified as variables. 19 Q. Quote, "Our findings on talc 20 and endometriosis are consistent with 21 previous findings and compatible with the 22 hypothesis that these factors increase 23 the risk of ovarian cancer and that 24 inflammation may be a common pathway."</p>	<p style="text-align: right;">Page 237</p> <p>1 should have it. 2 (Document marked for 3 identification as Exhibit 4 Mossman-23.) 5 BY MR. SMITH: 6 Q. Is Merritt 2008 one of the 7 studies that you relied on in the basis 8 of your opinions in this case? 9 A. Let me just look at it just 10 to make sure. 11 Q. I can't remember if I 12 attached that reference. 13 A. No. 14 Q. I did your updated, but I'm 15 going to attach this as Exhibit 23, the 16 original key references and reliance 17 materials. I attached the amended one 18 earlier. 19 Doctor? 20 A. Yes. 21 Q. Did you rely on Merritt to 22 form the basis of your opinions in this 23 case? 24 A. No, I did not.</p>

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<p style="text-align: right;">Page 238</p> <p>1 Q. And from that paper, quote, 2 "Chronic inflammation has been proposed 3 as a possible causal mechanism that 4 explains the observed association between 5 certain risk factors, such as the use of 6 talcum powder, talc, in the pelvic region 7 and epithelial ovarian cancer." 8 Would you agree or disagree 9 with that statement from Merritt? 10 MR. FROST: Objection. 11 THE WITNESS: I'd have to 12 see the paper to see in which 13 context it was used and also what 14 reference was supplied. 15 Again, I think the key word 16 here is "possible." So I'm not 17 aware that this paper presented 18 any causative role or causative 19 link between talcum powder and 20 ovarian cancer. 21 BY MR. SMITH: 22 Q. Well, do you -- are you of 23 the opinion that chronic inflammation is 24 a possible causal mechanism to ovarian</p>	<p style="text-align: right;">Page 240</p> <p>1 only one, I think, compelling 2 study that indicates that chronic 3 inflammation is not a causal 4 mechanism. Let me emphasize that 5 I also have looked at the 6 meta-analysis on pelvic 7 inflammatory disease that show 8 that this is not linked to ovarian 9 cancer, as well as the data on 10 aspirin and NSAIDs. 11 BY MR. SMITH: 12 Q. That wasn't -- my question 13 wasn't about whether it shows a causal 14 relationship. My question is, to you, 15 are you of the opinion chronic 16 inflammation is a possible mechanism 17 leading to the development of ovarian 18 cancer? 19 MR. FROST: Objection to 20 form. 21 THE WITNESS: Well, yeah, 22 and as I said previously, the data 23 suggests that it is not a possible 24 mechanism that leads to the</p>
<p style="text-align: right;">Page 239</p> <p>1 cancer? 2 MR. FROST: Objection to 3 form. 4 THE WITNESS: I would argue 5 against that based upon the 6 literature that I reviewed. We 7 can go into that later or we can 8 go into it now. 9 BY MR. SMITH: 10 Q. I'm just asking, do you 11 think chronic inflammation is a possible 12 mechanism leading to the development of 13 ovarian cancer? 14 A. Not based upon what I've 15 read or seen regarding Dr. Shih's work in 16 this regard. 17 Q. Dr. Shih's work? Is that 18 the basis of your opinion that chronic 19 inflammation is not a possible mechanism 20 leading to the development of ovarian 21 cancer? 22 MR. FROST: Objection to 23 form. 24 THE WITNESS: No, that's</p>	<p style="text-align: right;">Page 241</p> <p>1 development of disease. 2 BY MR. SMITH: 3 Q. Quote -- the next quote -- 4 And you say that the data 5 suggest that. What data are you talking 6 about? What work? Is this an expert 7 report? Is Shih an expert report? 8 MR. FROST: Objection to 9 form. 10 THE WITNESS: No. As I 11 said, the Shih study is only one 12 of many studies beginning at the 13 cell level, indicating in my own 14 work that talc does not give rise 15 to genes that induce chronic 16 inflammation. 17 Also the studies in animals 18 indicate that there is no chronic 19 inflammation associated with 20 disease development. 21 The pelvic inflammatory 22 disease literature and the 23 literature on aspirin and NSAIDs, 24 Dr. Shih's study examines this</p>

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<p style="text-align: right;">Page 242</p> <p>1 directly and is compelling</p> <p>2 evidence that chronic inflammation</p> <p>3 does not lead to the causation of</p> <p>4 ovarian cancers.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Where -- I'm looking on your</p> <p>7 reliance materials. Where is</p> <p>8 Dr. Shih's -- where is Dr. Shih listed on</p> <p>9 here?</p> <p>10 A. Dr. Shih's study was one</p> <p>11 that I read after I compiled my opinions;</p> <p>12 that is, my final report in this case.</p> <p>13 Q. When did you read that?</p> <p>14 A. I read that within the last</p> <p>15 two weeks.</p> <p>16 Q. Well, you provided me an</p> <p>17 updated list of materials relied upon.</p> <p>18 It's not in that.</p> <p>19 A. It should have been.</p> <p>20 Q. Is it?</p> <p>21 A. Yes.</p> <p>22 MR. FROST: It should be.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. I see. It says "Expert</p>	<p style="text-align: right;">Page 244</p> <p>1 And yes, it is a compelling study</p> <p>2 showing that there is no</p> <p>3 inflammation associated with early</p> <p>4 lesions in ovarian cancers.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. It's not a study, ma'am.</p> <p>7 It's an expert report. It's not peer</p> <p>8 reviewed, correct?</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: I'm sorry. As</p> <p>11 a pathologist, I looked at that</p> <p>12 data. It should be a</p> <p>13 peer-reviewed report and maybe</p> <p>14 some day.</p> <p>15 But the fact is, it was</p> <p>16 beautifully done and it was</p> <p>17 compelling data showing that</p> <p>18 inflammation is not associated</p> <p>19 with early intraepithelial</p> <p>20 development in serous types of</p> <p>21 cancers.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Ma'am, one day I might be</p> <p>24 president of the United States.</p>
<p style="text-align: right;">Page 243</p> <p>1 report of Shih."</p> <p>2 A. That's what I'm talking</p> <p>3 about.</p> <p>4 Q. That's a defense expert</p> <p>5 report?</p> <p>6 A. That's correct.</p> <p>7 Q. So one of the major bases of</p> <p>8 whether talc can cause chronic</p> <p>9 inflammation that could possibly lead to</p> <p>10 the development of ovarian cancer, one of</p> <p>11 your major reliance materials is an</p> <p>12 expert report for the defendants in this</p> <p>13 litigation?</p> <p>14 MR. FROST: Objection.</p> <p>15 THE WITNESS: That's not</p> <p>16 what I said.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. You said it was a compelling</p> <p>19 study that you relied upon for that</p> <p>20 opinion.</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: It bolstered</p> <p>23 my preexisting opinions written in</p> <p>24 my report before I saw the study.</p>	<p style="text-align: right;">Page 245</p> <p>1 My question to you is, is</p> <p>2 that a peer-reviewed publication?</p> <p>3 MR. FROST: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: As I read it,</p> <p>6 no. But I'm sure it will be some</p> <p>7 day.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. Okay. What do you base your</p> <p>10 opinion on, "I'm sure it will be some</p> <p>11 day"? What do you base that on?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Dr. Shih is an</p> <p>14 international expert in this</p> <p>15 field. A leading pathologist in</p> <p>16 this field. And, therefore, this</p> <p>17 study is at a high -- I would call</p> <p>18 it a highly ranked, thorough study</p> <p>19 done beautifully by leading</p> <p>20 pathologists in this field.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. All those accolades gave</p> <p>23 by -- given by another defense expert</p> <p>24 being paid in this litigation, correct?</p>

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<p style="text-align: right;">Page 246</p> <p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: I am not 4 certain to whether how much he or 5 she is being paid. I'm not 6 looking at the report as a report, 7 per se. I'm looking at the data 8 and assessing it scientifically, 9 and it is compelling data. 10 BY MR. SMITH: 11 Q. I meant all the accolades 12 that you're throwing on this expert 13 report are by you, who is a defense paid 14 expert and been in talc litigation since 15 2014; is that correct, Dr. Mossman? 16 A. No, it's -- 17 MR. FROST: Objection -- 18 BY MR. SMITH: 19 Q. That's not correct? Let's 20 break it down then. 21 A. No, let -- let me finish. 22 Q. Okay. 23 A. I'm not talking as an expert 24 for defense in litigation. I'm talking</p>	<p style="text-align: right;">Page 248</p> <p>1 BY MR. SMITH: 2 Q. Studied the field of talc 3 and ovarian cancer for 40 years? 4 A. No. 5 MR. FROST: Objection. 6 THE WITNESS: Who studied 7 the field of ovarian cancer most 8 recently. But who has done 9 research on development of 10 epithelial cancers in the cervix, 11 in the skin, and in the lung. 12 BY MR. SMITH: 13 Q. That's not what we are 14 about. We're talking about ovarian 15 cancer. I'm not talking about the cervix 16 or the lung -- I'm not talking about 17 cervical cancer. 18 Do you understand that? I'm 19 talking about ovarian cancer. 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: What I'm 23 saying is that inflammation is 24 inflammation regardless of the</p>
<p style="text-align: right;">Page 247</p> <p>1 as a pathologist in the study of science. 2 This was a scientific study, 3 and it was done correctly and it is very 4 important in terms of bolstering my 5 opinions which were linked to other 6 things prior to my seeing the Shih study. 7 Q. Ma'am, it's an expert 8 report. Your reliance materials have you 9 here as a paid expert for Johnson &amp; 10 Johnson who is a defendant in the 11 litigation. You've been paid for talc 12 litigation since 2014. So your opinions 13 and your reliance materials and your 14 opinion in this case is for litigation. 15 Do you not understand that? 16 MR. FROST: Objection to 17 form. 18 THE WITNESS: Yes. And I 19 think you are incorrect. My 20 opinions are not as expert in 21 litigation. 22 My opinions are as a 23 scientist who has studied this 24 field for 40 years.</p>	<p style="text-align: right;">Page 249</p> <p>1 cancer that you're talking about. 2 BY MR. SMITH: 3 Q. So inflammation is 4 inflammation. 5 A. What I'm saying here is that 6 there is no evidence that chronic 7 inflammation is associated with the 8 causation or early development of ovarian 9 cancers. 10 Q. You have not performed one 11 study on cosmetic-grade talc, correct? 12 A. I have said that before, 13 yes. 14 Q. You have not performed one 15 study on Shower to Shower or Baby Powder 16 which are the products at issue in this 17 case, correct? 18 MR. FROST: Objection to 19 form. 20 THE WITNESS: As I 21 emphasize, I have looked at 22 industrial talcs -- 23 BY MR. SMITH: 24 Q. No, ma'am. That's not</p>

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<p style="text-align: right;">Page 250</p> <p>1 responsive to my question.  2 My question is, have you  3 performed any studies on Baby Powder and  4 Shower to Shower that are at issue in  5 this litigation?  6 MR. FROST: Objection to  7 form.  8 THE WITNESS: I have not  9 myself performed studies.  10 BY MR. SMITH:  11 Q. And have you performed  12 studies on the types of asbestos that  13 experts have found and internal documents  14 have revealed from Johnson &amp; Johnson and  15 Imerys that are in Baby Powder and Shower  16 to Shower?  17 MR. FROST: Objection.  18 THE WITNESS: Again, I've  19 looked at talc, fibrous talc,  20 which contained non-asbestiform  21 tremolite. And I'm unaware of  22 scientific data supporting the  23 claims that tremolite,  24 anthophyllite, or actinolite</p>	<p style="text-align: right;">Page 252</p> <p>1 ovarian cancer."  2 Would you agree or disagree  3 with that statement from Merritt?  4 MR. FROST: Objection.  5 THE WITNESS: I don't have  6 it in front of me. I -- I really  7 can't comment on it.  8 BY MR. SMITH:  9 Q. You can't comment on that  10 quote, whether you agree with that  11 statement or not?  12 A. Which one was this now? The  13 chronic inflammation again?  14 Q. It's the second one.  15 "Chronic inflammation was first invoked  16 as a possible mechanism leading to the  17 development of epithelial ovarian cancer  18 to explain observed associations between  19 certain factors such as talcum powder in  20 the perineal region or pelvic  21 inflammatory disease, PID, and a risk of  22 ovarian cancer."  23 Do you agree or disagree  24 with that statement?</p>
<p style="text-align: right;">Page 251</p> <p>1 asbestos are in talcs.  2 MR. SMITH: Object to  3 nonresponsiveness.  4 BY MR. SMITH:  5 Q. My question is, have you  6 ever performed a study on the types of  7 asbestos that we went through earlier  8 that have been found in the internal  9 documents of Johnson &amp; Johnson and Imerys  10 that are in Baby Powder and Shower to  11 Shower and by experts that have tested  12 Baby Powder bottles?  13 MR. FROST: Objection.  14 THE WITNESS: I have not.  15 BY MR. SMITH:  16 Q. Okay. In the Merritt --  17 another Merritt quote here. "Chronic  18 inflammation was first invoked as a  19 possible mechanism leading to the  20 development of epithelial ovarian cancer  21 to explain observed associations between  22 certain factors such as talcum powder in  23 the perineal region or pelvic  24 inflammatory disease and the risk of</p>	<p style="text-align: right;">Page 253</p> <p>1 MR. FROST: Objection to  2 form.  3 THE WITNESS: I disagree  4 with the statement.  5 BY MR. SMITH:  6 Q. Thank you.  7 Next Merritt quote:  8 "Indeed, the most consistent evidence  9 linking inflammation with ovarian cancer  10 comes from many reports that use of the  11 talc in the perineal region increases  12 ovarian cancer risk."  13 Would you agree or disagree  14 with that statement from Merritt?  15 MR. FROST: Objection.  16 THE WITNESS: Again, I'd  17 have to see the report and see the  18 references, but the references  19 that I have reviewed suggest that  20 this is not consistent evidence at  21 all.  22 BY MR. SMITH:  23 Q. And have you read Gates or  24 did you rely on Gates 2008 for the basis</p>

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<p>1 of your opinion in this case?</p> <p>2 A. It was one of the cohort</p> <p>3 studies I believe.</p> <p>4 Q. She has several.</p> <p>5 A. I'd have to see the</p> <p>6 publication.</p> <p>7 Do you have it?</p> <p>8 MR. FROST: Reliance list.</p> <p>9 Did you check your reliance list?</p> <p>10 THE WITNESS: I mean, I have</p> <p>11 to see the publication itself.</p> <p>12 MR. FROST: Sure.</p> <p>13 MR. SMITH: I'll get that at</p> <p>14 a break. Yeah, I'll get that at a</p> <p>15 break. Let me see if I can find</p> <p>16 it real quick. If not, I'll move</p> <p>17 on. I'll come back to it.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. But, quote, "Talc particles</p> <p>20 can induce an inflammatory response in</p> <p>21 vivo which may be important" -- what's</p> <p>22 "in vivo" mean?</p> <p>23 A. It means in the body.</p> <p>24 Q. "Talc particles can induce</p>	<p>1 I believe that no normal ovarian</p> <p>2 cells treated with talc undergo</p> <p>3 increased cell proliferation,</p> <p>4 neoplastic transformation, and</p> <p>5 generation of reactive oxygen</p> <p>6 species.</p> <p>7 She may be referencing</p> <p>8 another study which -- by</p> <p>9 Buz'Zard, et al., that encompasses</p> <p>10 these ideas.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. I'm -- going to have to look</p> <p>13 at the screen now. I just don't have --</p> <p>14 I don't know what happened with the -- I</p> <p>15 apologize.</p> <p>16 Did you rely on Langseth</p> <p>17 2008 for the basis of your opinions in</p> <p>18 this case?</p> <p>19 A. I did. It was an</p> <p>20 epidemiological study. Again, the</p> <p>21 hypothesis, mechanism of carcinogenicity</p> <p>22 may be related to inflammation. He</p> <p>23 didn't look at inflammation, but it's a</p> <p>24 hypothesis that he put forth.</p>
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<p>1 an inflammatory response in vivo."</p> <p>2 Do you agree with that?</p> <p>3 MR. FROST: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: I believe we</p> <p>6 talked about that with talc</p> <p>7 pleurodesis, yes.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. -- "which may be important</p> <p>10 in ovarian cancer risk. Normal ovarian</p> <p>11 cells treated with talc are more likely</p> <p>12 to undergo cell proliferation and</p> <p>13 neoplastic transformation, and cellular</p> <p>14 generation of reactive oxygen species</p> <p>15 increases with increasing exposure to</p> <p>16 talc."</p> <p>17 Do you agree with that</p> <p>18 statement from Gates?</p> <p>19 MR. FROST: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: Gates did not</p> <p>22 show that in this publication. I</p> <p>23 do remember the statement. And I</p> <p>24 would not agree with the statement</p>	<p>1 Q. Do you believe it's a</p> <p>2 possible hypothesis?</p> <p>3 MR. FROST: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: Based upon my</p> <p>6 studies with talc, no. Because in</p> <p>7 ovarian epithelial cells and</p> <p>8 certainly in pleural -- I should</p> <p>9 say peritoneal mesothelial cells</p> <p>10 we documented antiinflammatory</p> <p>11 effects of talc. So it's</p> <p>12 difficult for me to reconcile my</p> <p>13 findings with this statement.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. Collectively -- well, let me</p> <p>16 ask you this. Did you read the Mills</p> <p>17 2004 paper as reliance for your opinions</p> <p>18 in this case?</p> <p>19 A. Let me look here and see</p> <p>20 whether I did read it.</p> <p>21 No, I am uncertain what that</p> <p>22 is.</p> <p>23 I believe it might be an</p> <p>24 epidemiology study, because it does ring</p>



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<p>1 a bell.</p> <p>2 Q. You don't have it as your</p> <p>3 reliance materials for the basis of your</p> <p>4 opinion in this case; is that correct?</p> <p>5 A. No, it's not listed.</p> <p>6 Q. "Collectively, these studies</p> <p>7 point to a possible etiologic role of</p> <p>8 talc in ovarian cancer via an</p> <p>9 inflammatory process at the site of the</p> <p>10 ovarian epithelium."</p> <p>11 Would you agree or disagree</p> <p>12 with that statement from Mills?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: Yeah, I would</p> <p>16 disagree that -- that has not been</p> <p>17 shown.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Have you read the Ness 2000</p> <p>20 study?</p> <p>21 A. I have. These are all</p> <p>22 hypotheses generating.</p> <p>23 I believe some of them are</p> <p>24 reviews of the field as well.</p>	<p>1 time in the literature.</p> <p>2 Q. It says, "At the same time,</p> <p>3 a growing body of epidemiological</p> <p>4 evidence suggest that factors calling</p> <p>5 epithelial inflammation are involved in</p> <p>6 ovarian carcinogenesis. Such factors</p> <p>7 include asbestos and talc exposures,</p> <p>8 endometriosis, and pelvic inflammatory</p> <p>9 disease."</p> <p>10 I take it that you don't</p> <p>11 agree with that statement of Ness in</p> <p>12 1999?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: I don't. I</p> <p>16 don't agree with "such factors</p> <p>17 include." Maybe they were at the</p> <p>18 time. But there have been a lot</p> <p>19 of papers published since then</p> <p>20 that suggest the opposite.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Same study. "Inflammation</p> <p>23 by its nature produces toxic oxidants</p> <p>24 meant to kill pathogens. These oxidants</p>
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<p>1 Q. Quote, "Inflammation</p> <p>2 involves rapid cell division, DNA</p> <p>3 excision and repair, oxidative stress,</p> <p>4 and high concentrations of cytokines</p> <p>5 and" --</p> <p>6 A. Prostaglandins.</p> <p>7 Q. I'm glad you pronounced it.</p> <p>8 -- "all of which are</p> <p>9 established promoters of mutagenesis."</p> <p>10 Would you agree with that</p> <p>11 statement?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: In a general</p> <p>14 context, yes. But it certainly</p> <p>15 hasn't been shown for talc,</p> <p>16 because talc doesn't induce</p> <p>17 mutations.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Have you relied on Ness 1999</p> <p>20 in forming the basis of your opinions in</p> <p>21 this case?</p> <p>22 A. Yes. It's somewhat</p> <p>23 outdated, but I think that this was a</p> <p>24 review of the state of the art at that</p>	<p>1 cause direct damage to DNA, proteins, and</p> <p>2 lipids and may, therefore, play a role in</p> <p>3 direct carcinogenesis."</p> <p>4 Do you agree with that</p> <p>5 statement?</p> <p>6 MR. FROST: Objection.</p> <p>7 THE WITNESS: Again, it's a</p> <p>8 general statement with regard to</p> <p>9 inflammation in general. I don't</p> <p>10 agree with it as it's been</p> <p>11 shown -- has not been shown to be</p> <p>12 important in ovarian cancer</p> <p>13 development.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. Same study. "Direct</p> <p>16 induction of inflammation as a result of</p> <p>17 endometriosis, talc and asbestos exposure</p> <p>18 and PID, as well as ovulation itself, may</p> <p>19 act to promote ovarian tumorigenesis."</p> <p>20 Do you agree with that</p> <p>21 statement from Ness?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: Again, it's an</p> <p>24 outdated paper that hasn't</p>

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<p style="text-align: right;">Page 262</p> <p>1 evaluated these studies that don't 2 support that mechanism of action. 3 BY MR. SMITH: 4 Q. Same study. "We have 5 reviewed the data suggesting that an 6 additional mechanism that may underlie 7 ovarian cancer is inflammation with 8 concomitant rapid DNA turnover and 9 defective repair." 10 Do you agree or disagree 11 with that statement? 12 MR. FROST: Objection. 13 THE WITNESS: Again, I -- it 14 may have been true in 1999, but 15 data do not support that as a 16 whole. 17 BY MR. SMITH: 18 Q. Okay. Well, let's talk 19 about data that might be more relevant. 20 And you would agree that this is 21 epidemiological data that we have gone 22 through regarding the inflammation that's 23 on Exhibit 24, correct? 24 MR. FROST: Objection.</p>	<p style="text-align: right;">Page 264</p> <p>1 stapled. 2 (Document marked for 3 identification as Exhibit 4 Mossman-25.) 5 BY MR. SMITH: 6 Q. All right. Exhibit 25, this 7 is a paper that was published in 2009. 8 Do you see that, Doctor? "Inflammation: 9 A Hidden Path to Breaking the Spell of 10 Ovarian Cancer." 11 Do you see that? 12 A. Yes. I am not familiar with 13 the journal Cell Cycle, but... 14 Q. By Shan and Liu. 15 And if you turn to the next 16 page -- well, let me ask you this. Is 17 this on your reference materials that 18 form the basis of your opinion in this 19 case? 20 A. No. And I'm unfamiliar with 21 the journal. So I'm not sure it would 22 have been referenced by PubMed or my 23 PubMed searches. 24 Q. Okay. Well, let's go to the</p>
<p style="text-align: right;">Page 263</p> <p>1 THE WITNESS: I would agree, 2 I'm sorry. Was that a question? 3 BY MR. SMITH: 4 Q. Been dealing with 5 epidemiological studies? 6 A. Have we talked about them? 7 Q. Yes. 8 A. Yes, we have. 9 Q. Excuse me. That are 10 included in Exhibit 24 that we went 11 through all the quotes. Those are 12 epidemiological studies that we went 13 through, correct? 14 MR. FROST: Objection. 15 THE WITNESS: The majority 16 of these are epidemiology studies, 17 yes, with the exception of the 18 Trabert study. 19 MR. FROST: Are these two 20 different ones? 21 MR. SMITH: No. 22 MR. FROST: Okay. 23 MR. SMITH: Same one. 24 MR. FROST: Just not</p>	<p style="text-align: right;">Page 265</p> <p>1 first page. "Inflammation: A hidden 2 path to breaking the spell of ovarian 3 cancer." Shan and Liu, the authors from 4 the department of pathology at the 5 University of Texas M.D. Anderson Cancer 6 Center, Houston, Texas. 7 Is M.D. Anderson Cancer 8 Center in Houston, Texas, a reputable 9 cancer center in the United States and 10 throughout the world? 11 MR. FROST: Objection. 12 THE WITNESS: It is. 13 BY MR. SMITH: 14 Q. Let's go to the first -- 15 let's go to the box, grey box to the left 16 above introduction. "Epithelial ovarian 17 cancer is a highly lethal gynecological 18 cancer for which overall prognosis has 19 remained poor over the past few decades. 20 A number of theories have been postulated 21 in an effort to explain the etiology of 22 epithelial ovarian cancer each of which 23 has been both applauded and doubted. Of 24 note, these theories likely are not</p>

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<p style="text-align: right;">Page 266</p> <p>1 mutually exclusive as they all converge 2 more or less on the role of inflammation 3 in promoting ovarian tumorigenesis." 4 Do you agree with that 5 statement? 6 MR. FROST: Objection. 7 THE WITNESS: Yes. That the 8 inflammation certainly has been 9 shown to be important in late 10 stage cancers, including ovarian. 11 BY MR. SMITH: 12 Q. That's not what it says, 13 Doctor. It says, "Of note, these 14 theories are likely not mutually 15 exclusive as they all converge more or 16 less on the role of inflammation in 17 promoting ovarian tumorigenesis," 18 correct? 19 A. Correct. 20 Q. Okay. 21 A. And promotion is not 22 initiation or causation. 23 Q. I understand. 24 A. So that's what I stated.</p>	<p style="text-align: right;">Page 268</p> <p>1 Q. Sure. 2 A. -- uncover where -- 3 Q. We're going to go through 4 it. We're going to go through it. 5 A. Okay. 6 Q. All right. 7 Introduction. "Epithelial 8 ovarian cancer, EOC, is the most common 9 subgroup of ovarian cancer. It's the 10 deadliest gynecological cancer in the 11 United States, accounting for more deaths 12 than all other gynecological cancers 13 combined." 14 And we went through that 15 earlier, correct? 16 A. Yes. 17 Q. "The high mortality rate for 18 epithelial ovarian cancer is a result of 19 technical obstacles to early detection of 20 the disease, a high prevalence of distal 21 metastasis at late stages of the 22 disease" -- and that's in 70 percent of 23 the cases it said. 24 "This latter property is</p>
<p style="text-align: right;">Page 267</p> <p>1 That in general, 2 inflammation has been linked to the 3 progression as well as the dissemination 4 of preexisting tumors. 5 Q. Okay. Let me continue. "In 6 this review we describe the latest 7 studies on the role of inflammation in 8 the initiation and progression of 9 epithelial ovarian cancer from three 10 major aspects: Physiologic functions of 11 a normal ovary, potential involvement of 12 the fallopian tube in the initiation of 13 epithelial ovarian cancer, and the strong 14 impact of cellular microenvironment on 15 the development of disease." 16 Now, that statement doesn't 17 just say progression. It says 18 initiation, correct? 19 MR. FROST: Objection. 20 THE WITNESS: We describe 21 the latest studies on the role of 22 inflammation initiation. I'd 23 like -- I'd have to read this -- 24 BY MR. SMITH:</p>	<p style="text-align: right;">Page 269</p> <p>1 probably attributable to the unique 2 peritoneal environment of the epithelial 3 ovarian cancer which facilitates 4 convenient seating of ovarian cancer 5 cells in the peritoneal cavity, which is 6 further aided by the constant flow of 7 peritoneal fluid." 8 Were you aware of that 9 statement prior to us reading it? 10 A. Could you refer -- you're 11 going a little fast. I'm just wondering 12 where you are. 13 Q. I'm at introduction. 14 A. Okay. 15 Q. And I'm about six lines 16 down, "This latter property is probably 17 attributable." 18 Do you see that? 19 A. The first paragraph? 20 Q. Under introduction. 21 A. Yep. 22 Q. It's after "70 percent of 23 the cases." 24 Are you aware of the unique</p>

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<p>1 environment of peritoneal -- the 2 peritoneal environment being unique for 3 epithelial ovarian cancer which 4 facilitates convenient seating of ovarian 5 cancer cells in the peritoneal cavity, 6 which is further aided by constant flow 7 of peritoneal fluid." 8 Were you aware of that 9 statement prior to us reading that now? 10 MR. FROST: Objection to 11 form. 12 THE WITNESS: Yeah. I'm 13 still lost in where you are here, 14 and whether there are references 15 to that statement. 16 BY MR. SMITH: 17 Q. Ma'am. Ma'am. I'm in 18 introduction. 19 A. Gotcha. 20 Q. On the first page. 21 A. Okay. 22 Q. Do you see, one, two, three, 23 four, five, six, seven lines down, you 24 see 70 percent of cases right there?</p>	<p>1 trends. 2 So I think the word unique 3 peritoneal environment is of 4 question to me. I don't know why 5 it would be unique. 6 BY MR. SMITH: 7 Q. Okay. "We call particular 8 attention to this 'open' environment to 9 which epithelial ovarian cancer is 10 exposed because it has resulted in a 11 myriad of characteristics specific to 12 epithelial ovarian cancer such as ease of 13 widespread cancer metastases" -- 14 "metastases in short period of time, 15 unique formation of ascites, and high 16 susceptibility of the ovarian surface 17 epithelium or OSE to peritoneal 18 inflammatory stimuli." 19 A. Again, I think by open 20 environment they are talking about the 21 peritoneum as a cavity with fluids in it. 22 I don't recall nor have I seen papers 23 suggesting that there is high 24 susceptibility of ovarian epithelial to</p>
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<p>1 Do you see 70 percent? 2 A. Yes. 3 Q. I'm reading the line right 4 after that. "This latter property is 5 probably attributable to the unique 6 peritoneal environment of epithelial 7 ovarian cancer which facilitates 8 convenient seating of ovarian cancer 9 cells in the peritoneal cavity, which is 10 further aided by the constant flow of 11 peritoneal fluid." 12 Were you aware of that fact 13 before we read it just now? 14 MR. FROST: Objection. 15 THE WITNESS: I was aware of 16 the importance of tumor 17 microenvironment on dissemination 18 of preexisting cancers. I'm not 19 sure whether -- how unique a 20 peritoneal environment is. Since 21 we have looked at the environment 22 of the peritoneum and the lung in 23 terms of cytokines in regard to 24 mesotheliomas and see very similar</p>	<p>1 peritoneal inflammatory stimuli. 2 Again, this is a -- not -- 3 not a paper with original results. It's 4 a hypothesis paper. I don't see any data 5 here supporting that, or any data at all 6 in this manuscript other than a figure 7 entitled, "Potential sources of 8 inflammatory stimuli." 9 Q. Go to the next page, please. 10 A. Mm-hmm. 11 Q. If you look down at the 12 bottom right. "Inflammation: Cellular 13 senescence in ovarian epithelial 14 microenvironment and ovarian cancer." 15 "As described above the 16 complex biology of OSE," which is ovarian 17 surface epithelium, "makes ovarian 18 epithelial cells exceedingly sensitive to 19 peritoneal inflammatory agents." 20 And they talk about the open 21 system on the page we read just before 22 that. Do you recall that? 23 A. Yeah, but again I want to 24 emphasize that they are talking about</p>

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<p style="text-align: right;">Page 274</p> <p>1 Figure 1, "Potential sources of 2 inflammatory stimuli." And there's no 3 data to support this hypothesis in the 4 paper. 5 Q. It doesn't say hypothesis 6 anywhere, does it, Doctor? 7 MR. FROST: Objection. 8 THE WITNESS: This is a 9 hypothesis paper. There's no data 10 in it. This is a figure that they 11 have drawn, a schematic in which 12 they are hypothesizing that there 13 is inflammatory stimuli in the 14 peritoneal fluids. 15 So I'm unclear as to the 16 data. I think it's an intriguing 17 hypothesis. But as I emphasized 18 previously, it hasn't been borne 19 out in the last decade. 20 BY MR. SMITH: 21 Q. Okay. Let's look at Figure 22 1. It has -- at the bottom right. It 23 has, "Peritoneal inflammatory stimuli, 24 initiation of premalignant ovarian</p>	<p style="text-align: right;">Page 276</p> <p>1 been described as one enriched with a 2 broad spectrum pro-inflammatory cytokines 3 and chemokines. Increasing evidence 4 suggests that inflammation contributes 5 significantly to the etiology of 6 epithelial ovarian cancer." 7 What does "etiology" mean? 8 A. Basically the process of 9 disease. 10 Again, there's no references 11 to support this. So I'm not sure what he 12 means by etiology. It's a very broad 13 term. 14 Q. Okay. Let's go to -- hold 15 on a second. Bear with me just a second. 16 Man, they did a weird way of 17 copying this stuff down there. I mean, 18 you talking about -- I couldn't figure it 19 out. It all just came to me. And I just 20 can't believe what I'm seeing. But 21 anyway, we'll get it straight. 22 MR. FROST: Is this one 23 copy? 24 MR. SMITH: Yeah, I'm</p>
<p style="text-align: right;">Page 275</p> <p>1 epithelial cells, senescent fibroblasts, 2 inflammatory cells, and capillaries." 3 Do you see that diagram in 4 Figure C? 5 A. Yes. 6 Q. And it says under Figure 1, 7 "Potential sources of inflammatory 8 stimuli that may contribute to the 9 initiation and/or progression of 10 epithelial ovarian cancer." 11 Do you see that? 12 A. I do. And it also states 13 that these functions may be 14 pro-inflammatory in nature. 15 So, again, this is an 16 intriguing hypothesis, but it was in 17 2009. And in ten years there's no 18 evidence suggesting that this hypothesis 19 is true. 20 Q. We'll get to that. Let's go 21 to the page, the last page conclusions. 22 A. Okay. 23 Q. "The tumor milieu in which 24 epithelial ovarian cancer develops has</p>	<p style="text-align: right;">Page 277</p> <p>1 getting ready to hand it to you 2 now. 3 (Document marked for 4 identification as Exhibit 5 Mossman-26.) 6 (Whereupon, a discussion was 7 held off the record.) 8 BY MR. SMITH: 9 Q. Okay. Doctor, this is a 10 study not from back in time. This is 11 August 2018, a year ago, correct? 12 A. Yes. It's in another 13 journal that I have never heard of. So 14 I'm just trying to see whether it would 15 have appeared on my PubMed searches. 16 Q. Down at the bottom left, it 17 has NCBI, which is the public release of 18 government -- and it has NIH.gov. What 19 is NIH? 20 A. That means it's referenced 21 in the National Institutes or National 22 Library of Medicine. 23 Q. It's the National Institute 24 of Health, correct?</p>

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<p style="text-align: right;">Page 278</p> <p>1 A. NIH is the National 2 Institutes of Health. I don't think the 3 study was done at the National Institutes 4 of Health. 5 Q. And this study is entitled 6 The Role of Inflammation and Inflammatory 7 Mediators in the Development, 8 Progression, Metastasis and 9 Chemoresistance of Epithelial Ovarian 10 Cancer, correct? 11 A. Yes. This appears to be 12 another review with no new data. Allow 13 me to just go through this. 14 Q. I'm going to read some 15 sections in the abstract. "Inflammation 16 plays a role in the initiation and 17 development of many types of cancers, 18 including epithelial ovarian cancer (EOC) 19 and high-grade serous ovarian cancer 20 (HGSC), a type of epithelial ovarian 21 cancer." 22 Do you agree or disagree 23 with that statement in the abstract of 24 this paper?</p>	<p style="text-align: right;">Page 280</p> <p>1 A. Prostaglandins. 2 Q. Thank you. 3 -- "prostaglandins, and 4 growth factors that contribute to 5 increase cell division and genetic and 6 epigenetic changes." 7 Do you agree with those 8 statements? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: I believe that 12 this is a generalized statement in 13 terms of epithelial cells, but not 14 with regard to ovarian epithelial 15 cells. 16 BY MR. SMITH: 17 Q. "These exposure-induced 18 changes promote" -- we just went through 19 that. "Furthermore, the pro-inflammatory 20 tumor microenvironment (TME) contributes 21 to epithelial ovarian cancer and 22 metastases" -- 23 A. Metastases. 24 Q. I don't know why I'm</p>
<p style="text-align: right;">Page 279</p> <p>1 A. I disagree. This is a 2 review. And I don't believe that 3 inflammation has been linked to the 4 initiation of epithelial ovarian cancers 5 or serous grades. 6 Q. Okay. 7 A. So I would -- I think it's 8 an emphatic statement that needs to be 9 referenced. 10 Q. There are -- this is the 11 abstract. "There are connections" -- and 12 we'll get to it. 13 A. Okay. 14 Q. "There are connections 15 between epithelial ovarian cancer in both 16 peritoneal and ovulation-induced 17 inflammation. Additionally, epithelial 18 ovarian cancers have an inflammatory 19 component that contributes to their 20 progression. At sites of inflammation, 21 epithelial cells are exposed to increased 22 levels of inflammatory mediators, such as 23 reactive oxygen species, cytokines" -- 24 pronounce that for me, please.</p>	<p style="text-align: right;">Page 281</p> <p>1 tripping over my words today. 2 -- "and chemo resistance. 3 In this review, we will discuss the roles 4 inflammation and inflammatory mediators 5 play in the development, progression, 6 metastases and chemoresistance of 7 epithelial ovarian cancer." 8 Correct? 9 MR. FROST: Objection to 10 form. 11 THE WITNESS: Yes, this is a 12 review that discusses that. 13 BY MR. SMITH: 14 Q. Okay. And the first 15 paragraph is, "Inflammation and 16 epithelial ovarian cancer." 17 Do you see that? 18 A. I do. 19 Q. And it states, "Inflammation 20 is part of the immune response that 21 protects against foreign pathogens and 22 aids in healing. Inflammation is 23 elicited in response to cellular damage 24 by infection, exposure to foreign</p>

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<p style="text-align: right;">Page 282</p> <p>1 particles or pollutants or irritants, or  2 an increase in cellular stress. The  3 ultimate goal of the inflammatory  4 response is to restore tissue  5 homeostasis, either by destruction or  6 healing of the damaged tissue.  7 "The acute or immediate  8 inflammatory response involves  9 modification of the vasculature  10 surrounding the site of stress or damage  11 to increase blood flow. This alteration  12 is then followed by activation of innate  13 immune cells already present in the  14 tissue including macrophages, dendritic  15 cells (DC) and mast cells and an increase  16 in infiltration of additional innate  17 immune cells into the affected tissue."  18 Do you agree with that?  19 MR. FROST: Objection.  20 THE WITNESS: It's a  21 generalized statement for  22 inflammation, yes.  23 BY MR. SMITH:  24 Q. It says, "At sites of</p>	<p style="text-align: right;">Page 284</p> <p>1 A. I do.  2 Q. The next paragraph talks  3 about ovarian cancer. And it states --  4 one, two, three -- four lines down,  5 "Chronic inflammation is an important  6 risk factor associated with epithelial  7 ovarian cancer and high-grade serous  8 ovarian cancer (HGSC), the most malignant  9 subtype of epithelial ovarian cancer."  10 Do you agree with that?  11 A. I don't see a statement for  12 that. I know inflammation has been  13 associated with late stage tumors, but we  14 don't know what the role is in terms of  15 disease or protection from disease and  16 what is the function of this.  17 Q. "In this review, we will be  18 primarily focus on inflammation as a risk  19 factor for invasive epithelial ovarian  20 cancer, but have also included supportive  21 evidence from other ovarian cancer  22 subtypes studied that do not describe the  23 subtype of ovarian cancer and other tumor  24 types as indicated."</p>
<p style="text-align: right;">Page 283</p> <p>1 inflammation, there are high levels of  2 reactive oxygen species, cytokines,  3 chemokines, and growth factors that are  4 produced by the immune cells and other  5 cells in tissue."  6 Do you agree with that?  7 MR. FROST: Objection to  8 form.  9 THE WITNESS: I agree that  10 this may be true in chronic  11 inflammation or extremely high  12 exposures to very toxic agents.  13 So in that vein, I would agree  14 with it.  15 BY MR. SMITH:  16 Q. "Acute inflammation is  17 essential for the tissue homeostasis and  18 to protect against normal exposure to  19 pathogens. However, in certain cases,  20 the body is unable to resolve this  21 response or is subjected to repeated  22 stimulation, resulting in chronic  23 inflammation."  24 Do you agree with that?</p>	<p style="text-align: right;">Page 285</p> <p>1 And then they go through and  2 they talk about, on the next page --  3 well, they talk about signaling pathways  4 and transcription factors and innate  5 immune response. It talks about the  6 immune responses.  7 Number 2 on the next page  8 talks about inflammation as a risk factor  9 for epithelial ovarian cancer. It has  10 cites there. It talks about ovulation.  11 It talks about infection.  12 And then it says, "Other  13 sources of inflammation."  14 Do you see that on Page 4 of  15 39?  16 A. I do.  17 Q. And it says, "The other  18 causes of inflammation in the ovaries  19 and/or fallopian tubes are endometriosis,  20 obesity, polycystic ovarian syndrome or  21 PCOS, and talc exposure."  22 Do you agree with that?  23 MR. FROST: Objection to  24 this and the prior question which</p>

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<p>1 sort of bleed together.</p> <p>2 THE WITNESS: Yeah, again</p> <p>3 there's no reference for -- for</p> <p>4 this statement. So I -- I</p> <p>5 disagree with it. Because talc</p> <p>6 exposures have not been linked to</p> <p>7 inflammation in the ovaries. And</p> <p>8 I think I've covered all the</p> <p>9 information that I reviewed to</p> <p>10 reach that conclusion. So this is</p> <p>11 a review by cell biologists in a</p> <p>12 low-impact journal I've never</p> <p>13 heard from or seen before.</p> <p>14 But in looking at the</p> <p>15 original data which is not</p> <p>16 relevant --</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Whoa, whoa. Hold on a</p> <p>19 second. Low-impact journal. What do you</p> <p>20 base that on?</p> <p>21 A. I've never heard of Cancers.</p> <p>22 I've heard --</p> <p>23 Q. Listen -- how do you know</p> <p>24 what the -- tell me what the impact</p>	<p>1 the next page, Page 5 of 39. And you go</p> <p>2 three paragraphs down. It says, "Talc is</p> <p>3 a silicate mineral and exposure to it can</p> <p>4 cause inflammation of the ovaries and</p> <p>5 poses a risk hazard for the development</p> <p>6 of epithelial ovarian cancer."</p> <p>7 Do you agree with that</p> <p>8 statement or not?</p> <p>9 A. Let me look up Reference 45</p> <p>10 and I'll tell you.</p> <p>11 No.</p> <p>12 Q. "It has been proposed that</p> <p>13 talc from talcum powder used for dusting</p> <p>14 and from condoms in the vaginal</p> <p>15 diaphragms can migrate up the fallopian</p> <p>16 tubes in retrograde flow of fluids and</p> <p>17 mucus and get lodged in the ovaries.</p> <p>18 Tubal ligation, which is protective for</p> <p>19 epithelial ovarian cancer is thought to</p> <p>20 block the transport of talc from lower</p> <p>21 genital -- from the lower genital tract.</p> <p>22 Talc behaves as a foreign particle,</p> <p>23 triggering an inflammatory response and</p> <p>24 has two sites. The talc attracts</p>
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<p>1 factor is then, for this journal.</p> <p>2 A. If I haven't seen it, let me</p> <p>3 guess --</p> <p>4 Q. No, ma'am, I don't want a</p> <p>5 guess --</p> <p>6 A. -- it's going to be lower --</p> <p>7 Q. -- I want you to tell me</p> <p>8 what the impact factor for this journal</p> <p>9 is.</p> <p>10 A. We can look it up. Why</p> <p>11 don't we look it up?</p> <p>12 Q. No, ma'am. You said it was</p> <p>13 a low-impact journal and you said --</p> <p>14 A. I have never heard of it --</p> <p>15 Q. I understand.</p> <p>16 A. -- so, yes.</p> <p>17 Q. I understand. I want you to</p> <p>18 tell me what your basis -- your basis for</p> <p>19 that is because you've never heard of it.</p> <p>20 A. I have -- I am aware of all</p> <p>21 the cancer journals that are high profile</p> <p>22 and high impact. This is not one of</p> <p>23 them.</p> <p>24 Q. Okay. We'll go to page --</p>	<p>1 macrophages, which then try to</p> <p>2 phagocytose it. The macrophages then</p> <p>3 send chemotactic signals to other immune</p> <p>4 response mediators and initiate a wound</p> <p>5 healing. Since talc is not degraded by</p> <p>6 the body, it inhibits the wound healing</p> <p>7 process, resulting in chronic</p> <p>8 inflammation."</p> <p>9 Would you agree with those</p> <p>10 statements?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: No, and they</p> <p>13 are not supported by the</p> <p>14 references. We can go through</p> <p>15 these. But these statements</p> <p>16 aren't supported by the</p> <p>17 references.</p> <p>18 In fact, 47 is a paper by</p> <p>19 Muscat and Huncharek on perineal</p> <p>20 talc use and ovarian cancer, a</p> <p>21 critical review. It concludes</p> <p>22 that talc is not associated with</p> <p>23 ovarian cancer risk.</p> <p>24 BY MR. SMITH:</p>

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<p style="text-align: right;">Page 290</p> <p>1 Q. No, no, no.</p> <p>2 A. So --</p> <p>3 Q. Doctor, it says, "Talc,</p> <p>4 there is not a case for causality."</p> <p>5 A. Right.</p> <p>6 Q. The -- the study published a</p> <p>7 statistically significant increased risk</p> <p>8 of ovarian cancer from genital talc use.</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: No.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. It does not?</p> <p>13 A. Muscat and Huncharek do not</p> <p>14 make --</p> <p>15 Q. Paid experts from the</p> <p>16 defendants.</p> <p>17 A. Pardon me?</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Did you know that they were</p> <p>21 paid experts from the defendants when</p> <p>22 they wrote this paper?</p> <p>23 A. No --</p> <p>24 Q. Okay.</p>	<p style="text-align: right;">Page 292</p> <p>1 inconsistent statements that are not</p> <p>2 supported by the references they cite.</p> <p>3 Q. Doctor, did you use</p> <p>4 Huncharek and Muscat as a basis for your</p> <p>5 opinions in this case, this reference</p> <p>6 here?</p> <p>7 A. It was one of several</p> <p>8 reviews, yes.</p> <p>9 Q. And you are stating that</p> <p>10 that paper did not reveal a statistically</p> <p>11 significant increased risk of ovarian</p> <p>12 cancer from genital talc use?</p> <p>13 MR. FROST: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: I would go</p> <p>16 back to that paper and see how it</p> <p>17 was worded, but the conclusions of</p> <p>18 the authors were that talc did not</p> <p>19 play a role in the causation of</p> <p>20 ovarian cancers.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Did the epidemiological</p> <p>23 study that is referenced here of Muscat</p> <p>24 and Huncharek conclude that there was a</p>
<p style="text-align: right;">Page 291</p> <p>1 A. -- this was in 2008. And</p> <p>2 they concluded that there was not an</p> <p>3 association. Yet this individual is</p> <p>4 citing this reference to support the</p> <p>5 statement "talc behaves as a foreign</p> <p>6 particle triggering an inflammatory</p> <p>7 response." And it's wrong. The paper is</p> <p>8 wrong, and the references that it uses</p> <p>9 are wrong.</p> <p>10 Heller didn't show that.</p> <p>11 Henderson didn't show that. Henderson is</p> <p>12 an editorial.</p> <p>13 So I would really question</p> <p>14 the source of this supposed journal</p> <p>15 called Cancers that I've never heard of,</p> <p>16 while -- and we have --</p> <p>17 Q. Let me ask -- I'm sorry, I</p> <p>18 didn't mean to cut you off.</p> <p>19 A. Yeah.</p> <p>20 Q. Go ahead.</p> <p>21 A. But -- we can still spend</p> <p>22 time going through it, but it's not going</p> <p>23 to alter my opinion that these authors</p> <p>24 wrote a very sloppy paper with</p>	<p style="text-align: right;">Page 293</p> <p>1 statistically significant increased risk</p> <p>2 of ovarian cancer from genital talc use?</p> <p>3 A. I --</p> <p>4 MR. FROST: Objection to</p> <p>5 form.</p> <p>6 THE WITNESS: Yeah. I'd</p> <p>7 have to go back and look at the</p> <p>8 paper --</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Okay.</p> <p>11 A. -- to see whether that was</p> <p>12 stated as such.</p> <p>13 Q. Now, under NSAIDS and</p> <p>14 reduced risk of epithelial ovarian</p> <p>15 cancer.</p> <p>16 "Further connecting</p> <p>17 inflammation to the epithelial ovarian</p> <p>18 cancer are several studies that</p> <p>19 demonstrate the intake of nonsteroidal</p> <p>20 antiinflammatory drugs, or NSAIDs,</p> <p>21 specifically of aspirin, correlates</p> <p>22 adversely with the risk of epithelial" --</p> <p>23 A. Are we going back to this</p> <p>24 review in Cancers?</p>

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<p style="text-align: right;">Page 294</p> <p>1 Q. Yes.</p> <p>2 A. Or for --</p> <p>3 MR. FROST: Yeah, I was</p> <p>4 going to say, what page are you</p> <p>5 on?</p> <p>6 THE WITNESS: Yeah.</p> <p>7 MR. SMITH: I'm on Page 5.</p> <p>8 Excuse me. I'm right below where</p> <p>9 I was reading.</p> <p>10 MR. FROST: Oh, I see.</p> <p>11 Section 2.4?</p> <p>12 MR. SMITH: Yep.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. "Further connecting</p> <p>15 inflammation to epithelial ovarian cancer</p> <p>16 are several studies that demonstrate that</p> <p>17 intake of nonsteroidal antiinflammatory</p> <p>18 drugs, NSAIDs, specifically of aspirin,</p> <p>19 correlates inversely with risk of ovarian</p> <p>20 cancer and endometrial cancer," and it</p> <p>21 has cites there.</p> <p>22 Do you see that, Doctor?</p> <p>23 A. I do, and again these</p> <p>24 studies are controversial and the</p>	<p style="text-align: right;">Page 296</p> <p>1 point it to her?</p> <p>2 MR. SMITH: That's fine.</p> <p>3 THE WITNESS: Yeah. Okay.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. "Oxidative stress has also</p> <p>6 been shown to facilitate epigenetic</p> <p>7 mechanisms in many cancers including</p> <p>8 epithelial ovarian cancer."</p> <p>9 Would you agree or disagree</p> <p>10 with that statement?</p> <p>11 A. Let me look at Reference 86</p> <p>12 and see whether it makes sense.</p> <p>13 No that's not supported by</p> <p>14 that.</p> <p>15 Q. Okay.</p> <p>16 A. It's another misquote. It's</p> <p>17 talking about tumor suppressor genes in</p> <p>18 ovarian cancer.</p> <p>19 Q. You've never seen this</p> <p>20 document, and you haven't seen the</p> <p>21 document reference. So you don't know</p> <p>22 what it says, do you, Doctor?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: I can read the</p>
<p style="text-align: right;">Page 295</p> <p>1 statement that he puts forth does not</p> <p>2 agree with a lot of the studies.</p> <p>3 And let me check which ones</p> <p>4 he's referencing, but I wouldn't agree</p> <p>5 with this statement.</p> <p>6 Q. Okay. Go to Page 11 of 39,</p> <p>7 if you look at the bottom. It's 3.1.</p> <p>8 It's ROS and oxidative stress.</p> <p>9 Do you see it?</p> <p>10 A. I do.</p> <p>11 Q. And if you go to the -- one,</p> <p>12 two, three -- fourth paragraph. The</p> <p>13 paragraph at the bottom says, "Oxidative</p> <p>14 stress has also been shown to facilitate</p> <p>15 epigenetic mechanisms in many cancers,</p> <p>16 including epithelial ovarian cancer."</p> <p>17 Would you agree or disagree</p> <p>18 with that?</p> <p>19 MR. FROST: Objection.</p> <p>20 THE WITNESS: Let's go -- so</p> <p>21 we're on the third paragraph and</p> <p>22 what sentence are you talking</p> <p>23 about?</p> <p>24 MR. FROST: Do you mind if I</p>	<p style="text-align: right;">Page 297</p> <p>1 title.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Well, that's not the whole</p> <p>4 paper though, is it, Doctor?</p> <p>5 A. Epigenetic mechanisms.</p> <p>6 Okay. We're talking about tumor</p> <p>7 suppressor genes and methylation. It's</p> <p>8 an epigenetic mechanism. OS, I have no</p> <p>9 idea what that means.</p> <p>10 Q. Do you agree or disagree</p> <p>11 with the statement, "Oxidative stress has</p> <p>12 also been shown to facilitate epigenetic</p> <p>13 mechanisms in many cancers including</p> <p>14 epithelial ovarian cancer"?</p> <p>15 A. It looks like, to me, that</p> <p>16 this Reference 86 is talking about</p> <p>17 methylation of tumor suppression genes</p> <p>18 and is not exploring the oxidative stress</p> <p>19 by any agents on these genes.</p> <p>20 Q. Do you agree or disagree</p> <p>21 with the statement?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: I agree with</p> <p>24 oxidative stress has been shown to</p>

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<p>1 facilitate epigenetic mechanisms. 2 Again, I question whether 3 Reference 86 used oxidative stress 4 insults to look at methylation of 5 tumor suppressor genes. And I 6 doubt that they did from the 7 title. 8 BY MR. SMITH: 9 Q. You doubt they did. You 10 don't know, correct? 11 MR. FROST: Objection. 12 THE WITNESS: No. Unless 13 you have the paper. I'd be 14 delighted to look at it. 15 BY MR. SMITH: 16 Q. And the statement talks 17 about, "Oxidative stress has also been 18 shown to facilitate epigenetic mechanisms 19 in many cancers, including epithelial 20 ovarian cancer." 21 Would you agree with that? 22 MR. FROST: Objection. 23 THE WITNESS: No. I just 24 said that I don't agree with it,</p>	<p>1 A. I do. 2 Q. This is on Oncotarget. Are 3 you familiar with Oncotarget? 4 A. Yes, I reviewed for them. 5 Q. "Oxidative Stress in Female 6 Cancers." And you're a reviewer of this 7 publication, right? 8 A. I didn't review this 9 publication, no. 10 Q. You said that you were a 11 reviewer of this Oncotarget, correct? 12 A. Oncotarget is a journal, and 13 I review papers for Oncotarget 14 occasionally. I have not seen this 15 paper. 16 Q. Okay. And it states, 17 "Abstract: Breast, cervical, and ovarian 18 cancer are highly prevalent in women 19 worldwide. Environmental, hormonal, and 20 viral-related factors are especially 21 relevant in the development of these 22 tumors. These factors are strongly 23 related to oxidative stress through the 24 generation of reactive oxygen species."</p>
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<p>1 because I don't believe that that 2 statement is reflected in the 3 title of Number 86. So I'd have 4 to see the paper. 5 But based upon the 6 references that you've pointed me 7 to already, I am suspicious 8 whether it does or not. 9 MR. SMITH: Okay. Let's 10 see. I don't think I marked that 11 as an exhibit, did I? 12 MR. FROST: No. 13 MR. SMITH: I did something 14 with my exhibit stickers. 15 That's 26. 16 (Document marked for 17 identification as Exhibit 18 Mossman-27.) 19 BY MR. SMITH: 20 Q. I want to next -- this is 21 another 2018 article, and it has the NCBI 22 NN -- NLM, NIH.gov reference at the 23 bottom. 24 Do you see that, Doctor?</p>	<p>1 Would you agree with that? 2 MR. FROST: Objection. 3 THE WITNESS: These 4 factors -- okay. Environmental, 5 hormonal, and viral-related 6 factors. I don't know what 7 they're talking about here. But 8 they're -- 9 BY MR. SMITH: 10 Q. Okay. Well, we'll read the 11 whole abstract. 12 A. Okay. 13 Q. "The oxidative stress is 14 caused by an imbalance in the redox 15 status of the organism and is literally 16 defined as 'an imbalance between ROS 17 generation and its detoxification by 18 biological system, leading to the 19 impairment of damage repair by 20 cells/tissue.' 21 "The multi-step progression 22 of cancer suggests that oxidative stress 23 is involved in cancer initiation, 24 promotion, and progression. In this</p>

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<p style="text-align: right;">Page 302</p> <p>1 review, we describe role of oxidative 2 stress and the interplay with 3 environmental, host, and viral factors 4 related to breast, cervical, and ovarian 5 cancers, initiation, promotion and 6 progression. 7 "In addition, the role of 8 natural antioxidant compounds, human and 9 other, compounds for breast, cervical, 10 and ovarian cancers' prevention/treatment 11 is discussed." 12 Do you see that? 13 A. Yes. This is a review. 14 Q. Do you agree with that 15 abstract? 16 A. As what they're describing, 17 I'd have to assume that's what they're 18 describing and see the references that 19 support their statements. 20 Q. Go to the conclusions. It's 21 on Page 16 of 30, Doctor. 22 "Conclusions and remarks." 23 And if you go down five lines, and you go 24 all the way to the right, it says, "We</p>	<p style="text-align: right;">Page 304</p> <p>1 Do you agree with that 2 statement? 3 A. I do. And as I emphasized 4 previously, reactive oxygen species are 5 known to be important in development in 6 late stage tumor progression and 7 metastases. 8 Q. Of the ovary? 9 A. In late stage, yes. 10 Q. No, it doesn't say late 11 stage. It just says ovary. 12 A. It says development and 13 progression. That is not initiation. 14 Development is what happens in subsequent 15 stages of cancer development. And so, as 16 I emphasize, ovarian and other tumors may 17 be reflective of roles of late stage 18 cancer development induced by oxidative 19 stress or inflammation. Not causation. 20 (Document marked for 21 identification as Exhibit 22 Mossman-28.) 23 BY MR. SMITH: 24 Q. I marked that previous</p>
<p style="text-align: right;">Page 303</p> <p>1 reviewed." 2 MR. FROST: Brooke, you go 3 to -- ours doesn't say 16 or 4 whatever. 5 THE WITNESS: No. 6 MR. FROST: It's 283 -- 7 MR. SMITH: I'm sorry. 8 MR. FROST: -- 5. 9 BY MR. SMITH: 10 Q. And if you go down five 11 lines and go to the right, it says, "We 12 reviewed the recent progress." 13 Do you see that? 14 A. "Recent progress towards the 15 potential role." Okay. 16 Q. "We reviewed the recent 17 progress towards the potential role of 18 ROS and associated oxygen" -- excuse 19 me -- "oxidative stress in the 20 carcinogenesis" -- "in carcinogenesis 21 since they are involved in the 22 development and progression of several 23 human cancers, like cervical, breast and 24 ovary."</p>	<p style="text-align: right;">Page 305</p> <p>1 exhibit as 27. I'm going to mark the 2 next exhibit, which is 28. And this is 3 from the National Cancer Institute, 4 Center Data Access System. 5 And it's "Inflammation 6 Markers and Risk of Endometrial and 7 Ovarian Cancer." And this is in a study 8 that is ongoing, and the principal 9 investigator is Nicolas Wentzensen. 10 Do you know who he is? 11 A. No, I've never heard of him. 12 Q. He's deputy branch chief and 13 senior investigator for the NCI division 14 of cancer epidemiology and genetics, 15 clinical genetics branch. 16 Did you know that? 17 A. I didn't. 18 Q. Okay. And here's a study 19 that's ongoing at the NCI. And here is 20 the title and the summary. 21 "Title, Inflammation Markers 22 and Risk of Endometrial and Ovarian 23 Cancer. Epidemiology evidence suggests 24 that chronic inflammation plays an</p>

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<p>1 important role in the pathogenesis of the</p> <p>2 endometrial and ovarian cancers."</p> <p>3 Do you agree with that</p> <p>4 statement?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: Yes. In late</p> <p>7 stage disease.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. It says, "An important role</p> <p>10 in the" -- what does pathogenesis means?</p> <p>11 A. Pathogenesis means the</p> <p>12 development of lesions as they go from an</p> <p>13 initiated cell to later stages of cancer</p> <p>14 development. So pathogenesis does not</p> <p>15 encompass causation. It's the</p> <p>16 development of the tumors over periods of</p> <p>17 time. So it's the tissue changes that</p> <p>18 become evidenced after cancers are</p> <p>19 initiated.</p> <p>20 Q. "Chronic inflammation can</p> <p>21 induce rapid cell division, increasing</p> <p>22 the possibility of replication error,</p> <p>23 ineffective DNA repair, and subsequent</p> <p>24 mutation. Risk factors for endometrial</p>	<p>1 MR. FROST: This one was 28,</p> <p>2 or this one's 29?</p> <p>3 MR. SMITH: Excuse me. The</p> <p>4 last one was 28.</p> <p>5 (Document marked for</p> <p>6 identification as Exhibit</p> <p>7 Mossman-29.)</p> <p>8 BY MR. SMITH:</p> <p>9 Q. This is 29. This is a 2008</p> <p>10 article. It says, "Inflammation is a key</p> <p>11 contributor to ovarian cancer cell</p> <p>12 seating."</p> <p>13 Do you see that, Doctor?</p> <p>14 A. I do.</p> <p>15 Q. And if you flip to the --</p> <p>16 the last page on the conclusion. In the</p> <p>17 final paragraph, two, four, six, seven</p> <p>18 lines down. Far right. "Our data in a</p> <p>19 mouse model are consistent with the</p> <p>20 concept that most factors implicated in</p> <p>21 ovarian cancer incidence converge on</p> <p>22 inflammation as a common denominator."</p> <p>23 Do you agree or disagree</p> <p>24 with that statement?</p>
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<p>1 cancer: Unopposed estrogen use,</p> <p>2 anovulation, polycystic ovarian syndrome,</p> <p>3 excessive/prolonged menstruation,</p> <p>4 diabetes and obesity, and conditions</p> <p>5 associated with ovarian cancer:</p> <p>6 Ovulation, pelvic inflammatory disease,</p> <p>7 PCOS, endometriosis and exposure to talc</p> <p>8 and asbestos are associated with chronic</p> <p>9 inflammation."</p> <p>10 Would you agree with that?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: Again, this is</p> <p>13 a -- it looks like a grant</p> <p>14 application here. A proposed</p> <p>15 study. And I would not agree with</p> <p>16 the statement that exposure to</p> <p>17 talc is associated with chronic</p> <p>18 inflammation.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Okay.</p> <p>21 A. No.</p> <p>22 Q. Let's next go to --</p> <p>23 MR. SMITH: That's</p> <p>24 Exhibit 28.</p>	<p>1 A. A mouse model. Most of the</p> <p>2 factors...</p> <p>3 Q. They performed a mouse model</p> <p>4 in this study.</p> <p>5 A. Yes. Inflammation is a</p> <p>6 common denominator of the pathogenesis,</p> <p>7 especially late stage, and what these</p> <p>8 individuals are showing is that when</p> <p>9 cells are seated in metastases,</p> <p>10 inflammation becomes important. So</p> <p>11 that's not inconsistent with the role of</p> <p>12 oxidants or inflammation in late stage</p> <p>13 development or metastases of cancers,</p> <p>14 including ovarian.</p> <p>15 Q. It says, "Our data in a</p> <p>16 mouse model are consistent with the</p> <p>17 concept that most of the factors</p> <p>18 implicated in ovarian cancer incidence</p> <p>19 converge on inflammation as a common</p> <p>20 denominator. One successful path to</p> <p>21 ovarian cancer prevention has been</p> <p>22 controlling factors that induce</p> <p>23 inflammation, such as the use of oral</p> <p>24 contraceptives to suppress ovulation."</p>

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<p>1 Do you agree with that?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: I think there</p> <p>4 are many reasons that oral</p> <p>5 contraceptives become important,</p> <p>6 including estrogen. So it's one</p> <p>7 pathway.</p> <p>8 BY MR. SMITH:</p> <p>9 Q. "Epidemiologic data show</p> <p>10 that aspirin and other nonsteroidal</p> <p>11 antiinflammatory drugs, NSAIDs, can be</p> <p>12 beneficial in the prevention of multiple</p> <p>13 cancers, including ovarian. Although</p> <p>14 factors associated with the increased</p> <p>15 risk of cancer such as aging and</p> <p>16 menopause can't be prevented, the risk</p> <p>17 can be reduced by suppressing</p> <p>18 inflammation."</p> <p>19 Do you agree with that?</p> <p>20 A. Again, I agree with the</p> <p>21 general premise that it -- inflammation</p> <p>22 may be important in late stage disease.</p> <p>23 Q. They don't say late stage</p> <p>24 disease there, Doctor.</p>	<p>1 appeared, or are relevant to causation of</p> <p>2 ovarian cancer by talc.</p> <p>3 Q. Also, I marked as</p> <p>4 Exhibit 30.</p> <p>5 (Document marked for</p> <p>6 identification as Exhibit</p> <p>7 Mossman-30.)</p> <p>8 THE WITNESS: 30 is?</p> <p>9 MR. FROST: It's coming up.</p> <p>10 He hasn't handed it over yet.</p> <p>11 THE WITNESS: Okay.</p> <p>12 MR. SMITH: Another</p> <p>13 interesting copy job.</p> <p>14 BY MR. SMITH:</p> <p>15 Q. You are familiar with this</p> <p>16 study, are you not, Doctor?</p> <p>17 MR. FROST: Is that more</p> <p>18 than one copy or is it --</p> <p>19 MR. SMITH: Here you go.</p> <p>20 MR. FROST: Okay. Thank</p> <p>21 you.</p> <p>22 MR. SMITH: Yeah.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. This was listed in your</p>
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<p>1 MR. FROST: Objection.</p> <p>2 THE WITNESS: No. And they</p> <p>3 don't say causation either.</p> <p>4 They are talking about</p> <p>5 prevention, and there could be</p> <p>6 many ways in which inflammation</p> <p>7 feeds an already established</p> <p>8 tumor.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Exhibit 29, 28, or 27, were</p> <p>11 they in your -- or 26, were any of those</p> <p>12 in your reference materials that you</p> <p>13 relied on as a basis for your opinion in</p> <p>14 this case?</p> <p>15 A. Say that again slowly.</p> <p>16 Q. Just the exhibits that we</p> <p>17 just went through, 26 through 29, are</p> <p>18 those listed as -- as reference materials</p> <p>19 that form a basis for your opinion in</p> <p>20 this case?</p> <p>21 A. No. As I emphasized, I</p> <p>22 looked at peer-reviewed original data in</p> <p>23 these studies and performed searches with</p> <p>24 talc and asbestos. And none of these</p>	<p>1 updated reference materials, correct?</p> <p>2 A. Yes.</p> <p>3 Q. "Analgesic use" -- "use and</p> <p>4 ovarian cancer risk: An analysis of</p> <p>5 ovarian cancer cohort consortium,"</p> <p>6 Trabert. It's in 2018. This isn't a</p> <p>7 decade ago, is it?</p> <p>8 A. No. It's an update to their</p> <p>9 earlier study.</p> <p>10 Q. And it says conclusions on</p> <p>11 the second page. "This large,</p> <p>12 prospective analysis suggests that women</p> <p>13 who use aspirin daily have a slightly</p> <p>14 lower risk of developing ovarian cancer,</p> <p>15 10 percent lower than infrequent/nonuse,</p> <p>16 similar to the risk reduced" --</p> <p>17 "reduction observed in case-control</p> <p>18 analyses. The observed potential</p> <p>19 elevated risk for ten plus years of</p> <p>20 frequent aspirin and NSAID use require</p> <p>21 further study, but could be due to</p> <p>22 confounding by medical indications for</p> <p>23 use in variation and drug dosing."</p> <p>24 And you reviewed that prior</p>

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<p style="text-align: right;">Page 314</p> <p>1 to your deposition today; is that 2 correct? 3 A. I did. 4 Q. Okay. All right. Let's 5 talk about transmigration. 6 MR. FROST: One second. Do 7 you want to take a quick? 8 MR. SMITH: Sure. 9 MR. FROST: I can use the 10 restroom. 11 THE VIDEOGRAPHER: We're 12 going off the record. The time is 13 2:43. 14 (Short break.) 15 THE VIDEOGRAPHER: We are 16 going back on record. Beginning 17 Media File Number 4. The time is 18 2:54. 19 BY MR. SMITH: 20 Q. Okay. Doctor, this is going 21 to be one of those situations again. I 22 apologize. And I'm -- we can read the 23 front together, but we can't read the 24 back together.</p>	<p style="text-align: right;">Page 316</p> <p>1 But I've gone through and 2 taken quotes out of different studies. 3 You stated earlier that you 4 did not go through the draft screening 5 assessment of Health Canada, correct, 6 when we were talking about inflammation? 7 A. That's correct. 8 Q. And so, the quote, "This 9 evidence of retrograde transport supports 10 the biological plausibility of the 11 association between perineal talc 12 application and ovarian exposure." 13 Would you agree or disagree 14 with that statement? 15 MR. FROST: Objection to 16 form. 17 THE WITNESS: Yeah, I would 18 disagree. There's no evidence of 19 retrograde talc transfer. 20 BY MR. SMITH: 21 Q. And we went over, earlier 22 you had not reviewed Taher, and the quote 23 here, "Particles of talc appeared to 24 migrate into the pelvis and ovarian</p>
<p style="text-align: right;">Page 315</p> <p>1 And -- 2 MR. SMITH: Here. I'm going 3 to attach this as Exhibit 31. Am 4 I right? 31. 5 (Document marked for 6 identification as Exhibit 7 Mossman-31.) 8 MR. FROST: Yeah, sounds 9 right. I'm just going to -- 10 before you start, same set of 11 actions as last time. We object 12 to using a summary document 13 that -- 14 MR. SMITH: Sure. 15 MR. FROST: -- and we object 16 to you asking any questions about 17 documents without putting it in 18 front of her. 19 BY MR. SMITH: 20 Q. Okay. This is titled, 21 "Biological plausibility, migration and 22 translocation," and what I've done here 23 is -- and there's a back to it and I'm 24 going to show it to you in a second.</p>	<p style="text-align: right;">Page 317</p> <p>1 tissue causing irritation and 2 inflammation." 3 Would you agree or disagree 4 with that quote from Taher? 5 MR. FROST: Objection. 6 THE WITNESS: I would 7 disagree. This has not been shown 8 in -- certainly not in his 9 studies, which are 10 epidemiological. But in terms of 11 other studies as well. 12 BY MR. SMITH: 13 Q. And also in Taher below it, 14 "Transport of talc via peritoneal stroma 15 and presence of ovaries is documented." 16 Are you aware of studies 17 that document that fact? 18 MR. FROST: Objection. 19 THE WITNESS: There are 20 studies documenting talc in 21 ovaries. But not transported talc 22 via peritoneal stroma. 23 BY MR. SMITH: 24 Q. And Schildkraut, is that one</p>

80 (Pages 314 to 317)



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<p>1 of the reference materials that you 2 relied upon for your opinions in this 3 case? 4 A. I did look at Schildkraut. 5 I don't know whether I listed it or not, 6 but I recall the study. It's an 7 epidemiological study of African-American 8 populations. 9 Q. Yeah, it's not listed in 10 your key references or reliance 11 materials. 12 A. Oh. 13 Q. But you said you read it? 14 A. I -- I have looked at it in 15 the past, yes. 16 Q. And says, quote from that 17 article, "As most high grade serous 18 epithelial ovarian cancer but not 19 nonserous subtypes arise in the fallopian 20 tube. It is possible that direct 21 exposure through genital talc 22 specifically affects this disease 23 subtype." 24 That we had talked earlier</p>	<p>1 BY MR. SMITH: 2 Q. So you don't -- can't answer 3 my question? 4 A. I can't remember. I'd have 5 to go back and look and see whether -- 6 what were the results in terms of certain 7 subtypes of tumors. 8 Q. Well, you had told me 9 earlier that the cohorts which you mainly 10 relied on supported your position that 11 talc does not statistically significantly 12 increase the risk of ovarian cancer. And 13 you can't tell me that one of the -- if 14 one of the cohort studies that you're 15 relying on heavily for that -- for that 16 statement, that it showed that a 17 statistical significant increased risk of 18 a particular type of histology of ovarian 19 cancer? 20 MR. FROST: Objection. 21 THE WITNESS: If I recall 22 the Nurses' Health Study, the 23 original publication emphasized 24 more or a -- that there were more</p>
Page 319	Page 321
<p>1 about high grade serous epithelial 2 ovarian cancer thought to arise in the 3 fallopian tube; is that correct? 4 MR. FROST: Objection. 5 THE WITNESS: That's true. 6 But that statement doesn't, in his 7 report, doesn't support the 8 premise of direct exposure through 9 the genital tract. And it's 10 unclear to me how this would 11 affect specifically one disease 12 subtype. 13 BY MR. SMITH: 14 Q. Well, in the first Nurses' 15 Health Study, what was -- was there a 16 subtype of histological type of 17 epithelial ovarian cancer that showed a 18 statistical significant increased risk 19 from the genital use of talc? 20 MR. FROST: Objection to 21 form. 22 THE WITNESS: I'd have to go 23 back and look at that study 24 specifically.</p>	<p>1 of the serous high grade tumors 2 observed. But that was not of 3 statistical significance. 4 And in the later study, that 5 did not appear to be the case. 6 And I believe it was Gertig versus 7 Gates. But I'd have to go back 8 and look at the studies 9 specifically. 10 BY MR. SMITH: 11 Q. Same from -- and also 12 Schildkraut. Did you realize that 13 Dr. Schildkraut is a female? 14 A. No. 15 Q. Okay. 16 "Therefore, lung inhalation 17 of powder could be a biologically 18 plausible mechanism for the association 19 between nongenital body powder use and 20 the increased risk" -- "increased 21 epithelial ovarian cancer risk, 22 particularly nonserous epithelial ovarian 23 cancers." 24 Do you agree with that</p>

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<p>1 statement from Schildkraut?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: Oh. I don't.</p> <p>4 They did find an increase in</p> <p>5 nongenital body power -- powder</p> <p>6 use, but not genital body powder</p> <p>7 use in that study.</p> <p>8 And other studies have not</p> <p>9 supported the nongenital route as</p> <p>10 being important in -- in ovarian</p> <p>11 cancer risk.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Well, let me ask you about</p> <p>14 that. Let me attach which is the next</p> <p>15 numbered exhibit, Number 32.</p> <p>16 (Document marked for</p> <p>17 identification as Exhibit</p> <p>18 Mossman-32.)</p> <p>19 BY MR. SMITH:</p> <p>20 Q. I do have those stapled.</p> <p>21 This is entitled,</p> <p>22 "Translocation pathways for inhaled</p> <p>23 asbestos fibers."</p> <p>24 Do you see that, Doctor?</p>	<p>1 subjects exposed to asbestos."</p> <p>2 Do you see that?</p> <p>3 A. Let's see. Is it -- this</p> <p>4 also in the abstract?</p> <p>5 Q. No, it's in the conclusion</p> <p>6 on Page 6 of 8.</p> <p>7 A. Oh, okay.</p> <p>8 Q. It says, "Asbestos fibers</p> <p>9 are found basically in all organs in</p> <p>10 subjects exposed to asbestos."</p> <p>11 Do you see that?</p> <p>12 A. Yes.</p> <p>13 Q. So let's get back to our</p> <p>14 outline that we were going through with</p> <p>15 Schildkraut.</p> <p>16 It says, "It has been</p> <p>17 proposed that chronic inflammation</p> <p>18 resulting from exposure to body powder,</p> <p>19 whether through inhalation or through</p> <p>20 transvaginal route may exert a</p> <p>21 suppressive effect on adaptive immunity</p> <p>22 leading to increased risk of epithelial</p> <p>23 ovarian cancer."</p> <p>24 Do you agree or disagree</p>
Page 323	Page 325
<p>1 It's a 2008 paper, January 2008?</p> <p>2 A. Yes.</p> <p>3 Q. And if you flip to the</p> <p>4 conclusion, on Page 6 of 8. This has to</p> <p>5 do with inhalation and pathways for</p> <p>6 obviously asbestos fibers as it -- it</p> <p>7 talks about.</p> <p>8 In the -- excuse me. Let's</p> <p>9 go to the abstract at the very beginning.</p> <p>10 I'm sorry.</p> <p>11 "We discuss the</p> <p>12 translocation of inhaled asbestos fibers</p> <p>13 based on pulmonary and pleuropulmonary</p> <p>14 interstitial fluid dynamics. Fibers can</p> <p>15 pass the alveolar barrier and reach the</p> <p>16 lung interstitium via the paracellular</p> <p>17 route down a mass water flow due to</p> <p>18 combined osmotic and hydraulic pressure</p> <p>19 gradient."</p> <p>20 Do you see that?</p> <p>21 A. Yes.</p> <p>22 Q. And then in conclusion on</p> <p>23 Page 6 of 8, it says, "Asbestos fibers</p> <p>24 are found basically in all organs in</p>	<p>1 with that statement from Schildkraut?</p> <p>2 MR. FROST: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: I don't</p> <p>5 believe that a transvaginal</p> <p>6 route -- I'm not sure what is</p> <p>7 meant by that.</p> <p>8 But certainly, whether</p> <p>9 inflammation exerts a suppressive</p> <p>10 effect on adaptive immunity has</p> <p>11 not been shown in ovarian cancer.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Next paragraph. "The</p> <p>14 results of this study show that genital</p> <p>15 powder use was associated with ovarian</p> <p>16 cancer risk in African-American women,</p> <p>17 and are consistent with localized chronic</p> <p>18 inflammation in the ovary due to</p> <p>19 particles that travel through a direct</p> <p>20 transvaginal route."</p> <p>21 Do you agree or disagree</p> <p>22 with that statement?</p> <p>23 MR. FROST: Objection to</p> <p>24 form.</p>

<p style="text-align: right;">Page 326</p> <p>1 THE WITNESS: I disagree.</p> <p>2 Dr. Schildkraut did not look at</p> <p>3 the travel of particles to the</p> <p>4 ovary through a direct</p> <p>5 transvaginal route.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. And Houghton was one of the</p> <p>8 cohorts you said that you relied heavily</p> <p>9 on for your opinion that talc does not</p> <p>10 statistically increase the risk of</p> <p>11 ovarian cancer, correct?</p> <p>12 A. Yes.</p> <p>13 Q. And this is a quote from</p> <p>14 Houghton, if you see below that. "Talc</p> <p>15 particulates from perineal application</p> <p>16 have been shown to migrate to the</p> <p>17 ovaries."</p> <p>18 Do you agree or disagree</p> <p>19 with that statement?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: I'd have to</p> <p>22 look at her publication. I know</p> <p>23 she did not look at migration in</p> <p>24 her studies. So I couldn't agree</p>	<p style="text-align: right;">Page 328</p> <p>1 cancer. But not through pathways</p> <p>2 that are linked to translocation</p> <p>3 to the ovaries.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. What are you basing that</p> <p>6 opinion on?</p> <p>7 A. First of all, if you have a</p> <p>8 hysterectomy, you are removing the source</p> <p>9 or the site of tumor development. And</p> <p>10 you're also affecting hormonal states</p> <p>11 which might be important.</p> <p>12 So to extrapolate results</p> <p>13 from tubal ligation or hysterectomy to</p> <p>14 pathways where talc migrates to the</p> <p>15 ovaries can't be linked from these</p> <p>16 studies.</p> <p>17 Q. You -- you said that for</p> <p>18 hysterectomies, but what about tubal</p> <p>19 ligation?</p> <p>20 A. A tubal ligation may do a</p> <p>21 lot of things.</p> <p>22 Q. May?</p> <p>23 A. Yes. There's supplemental</p> <p>24 hormones that maybe have to be given as a</p>
<p style="text-align: right;">Page 327</p> <p>1 with that without seeing the</p> <p>2 reference that supports the fact</p> <p>3 that talc particulates may migrate</p> <p>4 to the ovaries. I have not seen</p> <p>5 data showing that.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Okay. And to go on in that</p> <p>8 paragraph. "Furthermore, tubal ligation</p> <p>9 and/or hysterectomy which would eliminate</p> <p>10 the pathway of talc particles to the</p> <p>11 ovaries are associated with a reduced</p> <p>12 cancer risk."</p> <p>13 Do you see that?</p> <p>14 MR. FROST: Objection to</p> <p>15 form.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. It's in the same paragraph.</p> <p>18 A. Yes.</p> <p>19 Q. Do you agree or disagree</p> <p>20 with that statement from Houghton?</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: I agree with</p> <p>23 the fact that tube ligation and</p> <p>24 hysterectomy would affect ovarian</p>	<p style="text-align: right;">Page 329</p> <p>1 result.</p> <p>2 Q. May have to be given or you</p> <p>3 know this? What -- where are you getting</p> <p>4 this from?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: From my</p> <p>7 experience when I was in the</p> <p>8 department of obstetrics and</p> <p>9 gynecology and working with a</p> <p>10 physician in this regard.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Wait, hold on. The</p> <p>13 department of obstetrics and gynecology,</p> <p>14 when and where?</p> <p>15 A. At the University of</p> <p>16 Vermont. I mentioned earlier that --</p> <p>17 Q. I understand.</p> <p>18 A. -- that's where I got my</p> <p>19 masters degree in cervical cancer</p> <p>20 induction.</p> <p>21 And I worked with a doctor</p> <p>22 who did a variety of procedures including</p> <p>23 publishing on tubal ligations.</p> <p>24 Q. So when you are getting your</p>

<p style="text-align: right;">Page 330</p> <p>1 masters, how long of a program was this</p> <p>2 with this doctor?</p> <p>3 A. With Dr. Ray, I started as</p> <p>4 an undergraduate working summers. So I</p> <p>5 would say a total of maybe five years.</p> <p>6 Q. So as a undergraduate and</p> <p>7 as a -- in your masters program, working</p> <p>8 with a doctor who is an OB/GYN and</p> <p>9 observing him do tubal ligations and --</p> <p>10 A. No. That's not what I'm</p> <p>11 saying.</p> <p>12 Q. Well, what --</p> <p>13 A. What I'm saying is that</p> <p>14 tubal ligation occurs because of damage</p> <p>15 to an ovary, infection in the pelvic</p> <p>16 area, including chronic infection. And</p> <p>17 if you remove or tie off the tubes, it's</p> <p>18 a way to curb these various diseases.</p> <p>19 Tubal ligations are not done</p> <p>20 to eliminate pathways of talc migration</p> <p>21 to the ovaries.</p> <p>22 Q. I don't think --</p> <p>23 A. This makes no sense.</p> <p>24 Q. I don't think that's what</p>	<p style="text-align: right;">Page 332</p> <p>1 that's citing studies of women that have</p> <p>2 had tubal ligations and looking at that,</p> <p>3 right?</p> <p>4 The -- the purpose of -- the</p> <p>5 purpose of the -- of the -- the women</p> <p>6 getting the tubal ligation wasn't to</p> <p>7 prevent talc from going to their ovaries,</p> <p>8 but they are looking at reduced cancer</p> <p>9 risk from women that have that in these</p> <p>10 studies, correct?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: What I -- you</p> <p>13 asked if I agreed with the</p> <p>14 statement. And tubal ligation is</p> <p>15 not -- doesn't eliminate the</p> <p>16 pathway of talc particles to the</p> <p>17 ovaries as a primary function of</p> <p>18 the procedure.</p> <p>19 So it's -- this is an</p> <p>20 epidemiological study. We're</p> <p>21 talking about plausible pathways</p> <p>22 of migration or translocation of</p> <p>23 particles to the ovaries. And</p> <p>24 what I'm saying here is that</p>
<p style="text-align: right;">Page 331</p> <p>1 they are saying. What -- tubal ligation</p> <p>2 can also be used to prevent pregnancy, as</p> <p>3 a form of birth control, right?</p> <p>4 A. Well, it's pretty severe.</p> <p>5 Yes.</p> <p>6 Q. I have heard a woman saying</p> <p>7 she is going to get her tubes tied after</p> <p>8 she has her third child. I've heard that</p> <p>9 routinely, have you not?</p> <p>10 A. Yes, but it also affects</p> <p>11 their hormonal status.</p> <p>12 What I'm saying is there are</p> <p>13 many repercussions to tubal ligations and</p> <p>14 they are not done to eliminate the</p> <p>15 pathway of talc particles to the ovaries.</p> <p>16 Q. I don't think that's what</p> <p>17 they are stating here. I think that</p> <p>18 what --</p> <p>19 A. Well, that's --</p> <p>20 Q. -- Houghton is stating is,</p> <p>21 furthermore, tubal ligation and</p> <p>22 hysterectomy, which would eliminate the</p> <p>23 pathway of talc particles to the ovaries</p> <p>24 are associated with a reduced risk and</p>	<p style="text-align: right;">Page 333</p> <p>1 there's no link between tubal</p> <p>2 ligation, hysterectomy, and</p> <p>3 pathways of talc particle</p> <p>4 migration to the ovaries.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. So you're telling me that if</p> <p>7 the theory is, and what's been stated in</p> <p>8 all of the stuff that I've read with you</p> <p>9 and attached as Exhibit 31, about</p> <p>10 transmigration from a woman dusting her</p> <p>11 perineum with Baby Powder or Shower to</p> <p>12 Shower, and its ascension up the -- the</p> <p>13 genital tract of a woman, through the</p> <p>14 fallopian tubes to the ovaries, that if I</p> <p>15 then ligate the fallopian tubes,</p> <p>16 therefore, preventing an open fallopian</p> <p>17 tube path to the ovary, that that would</p> <p>18 not prevent the passage of talc to the</p> <p>19 ovary?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: There's no</p> <p>22 evidence suggesting that talc</p> <p>23 particles migrate to the ovary, is</p> <p>24 what I'm saying.</p>

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<p>1 BY MR. SMITH: 2 Q. Well, we talked about Taher 3 earlier, the study that you hadn't seen 4 in 2018 regarding Health Canada. Do you 5 recall that? 6 A. That's a meta-analysis of an 7 unpublished paper. He did not look at 8 migration to the ovaries. 9 Q. Okay. And in that study it 10 says, "Women with prior ligation of the 11 fallopian tubes show a significant 12 reduction in risk against ovarian cancer 13 compared to hysterectomy." And then it 14 says, "In a recent meta-analysis, the 15 authors reported a negative association 16 of tubal ligation (27 studies) and 17 hysterectomy (15 studies) with the risk 18 of ovarian cancer. This negative 19 association was more apparent in women 20 who had surgery at an early stage. A 21 highly plausible mechanism for this 22 association, as suggested by the authors, 23 involves blocking of ascent of agents 24 such as talc to the ovaries."</p>	<p>1 Doctor, have you -- did you rely on 2 Huncharek 2007 and Langseth 2008 for your 3 opinions in this case? 4 A. I did. But not with regard 5 to talc migration to the ovaries, which 6 was not examined in any of these studies. 7 Q. Well, Langseth down here at 8 the bottom, quote, "The evidence of talc 9 migration of the ovaries lends 10 credibility to such a possible 11 association." 12 Would you agree or disagree 13 with that? 14 MR. FROST: Objection. 15 THE WITNESS: I would 16 disagree. His studies did not 17 show talc migration to the 18 ovaries. 19 BY MR. SMITH: 20 Q. Okay. And then we have 21 Mills in 2004, Gertig in -- did you rely 22 on Mills for migration opinions in this 23 case? I'm looking at the -- I'm sorry. 24 MR. FROST: I take it this</p>
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<p>1 Would you agree with that or 2 disagree with that statement from Taher? 3 MR. FROST: Objection. 4 THE WITNESS: I disagree 5 with the statement. There is no 6 evidence supporting a biological 7 plausibility of migration or 8 translocation of talc to the 9 ovaries. In fact, there's a lot 10 of information showing that that 11 doesn't exist. 12 BY MR. SMITH: 13 Q. So you don't believe in 14 retrograde menstruation in women? 15 MR. FROST: Objection. 16 THE WITNESS: I don't 17 believe in it? 18 BY MR. SMITH: 19 Q. Does it not exist? 20 A. It happens in a very small 21 proportion, and that's entirely different 22 than movement of an inert particle 23 through retrograde migration. 24 Q. And we can go through them.</p>	<p>1 is the back side of that sheet? 2 MR. SMITH: Yeah. 3 THE WITNESS: I'm looking. 4 BY MR. SMITH: 5 Q. Mills 2004 for migration in 6 this case? 7 A. Oh, he's -- here Mills is 8 mentioning migration from the vagina 9 through the peritoneal cavity to the 10 ovaries. No, I've never seen anything 11 showing that pathway through a peritoneal 12 cavity from the vagina to the ovaries, 13 no. 14 Q. Okay. And Gertig, did you 15 rely on that for any of your -- 16 A. I relied on it for the 17 epidemiology, not for the statement that 18 talc is able to migrate. 19 Q. And Ness 1999, we discussed 20 that. You've looked at those studies in 21 2000, correct? 22 A. Right. 23 Q. Is that correct? 24 A. That -- that's correct.</p>



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1 Those are outdated, and they're  
2 hypotheses papers that didn't look at  
3 migration directly.  
4 Q. What about Cramer '99 or  
5 Heller '96?  
6 A. Cramer found the same amount  
7 of material in ovarian -- I should say in  
8 the ovaries of individuals who did use  
9 and did not use talc. So I would not  
10 support that. His evidence has just been  
11 looking at -- by pathology. So I  
12 would -- he did not perform migration  
13 studies. Heller also did not.  
14 Q. You're saying that  
15 Dr. Cramer in 1999 found talc in people  
16 exposed and not exposed?  
17 MR. FROST: Objection.  
18 THE WITNESS: I have to look  
19 at -- yeah, that isn't what I  
20 said. He found that talc -- I  
21 believe it was talc -- was in  
22 ovarian tissues, and it didn't  
23 necessarily correlate with talc  
24 use. But I'd have to go back and

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1 transmigration in this case?  
2 A. Hamilton, I don't recall  
3 that paper. I'd have to look at it.  
4 Q. It says, "There is evidence  
5 of transport of particulate material into  
6 the female peritoneum by the transvaginal  
7 route in both human and animal studies."  
8 Would you agree or disagree  
9 with that?  
10 A. Where are you now? I'm  
11 sorry.  
12 No, I don't think that's  
13 been shown. The presence of talc has  
14 been shown. It doesn't correlate with  
15 talc use. But the pathway, if any, is  
16 unclear, and certainly not from the  
17 perineum.  
18 Q. "Direct communication  
19 between the external environment and the  
20 peritoneal cavity exist in the female via  
21 her genital tract."  
22 Would you agree with that?  
23 MR. FROST: Objection.  
24 THE WITNESS: I don't know

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1 look at that.  
2 BY MR. SMITH:  
3 Q. It --  
4 A. I could be confusing that  
5 with Heller without the papers in front  
6 of me.  
7 Q. And Heller '96, have you  
8 looked at those papers -- that paper,  
9 excuse me?  
10 A. I did. And again, it's  
11 looking at what's there in the ovary and  
12 not how it got there. And that's true of  
13 Cramer as well. These are pathology  
14 studies.  
15 Q. What about Hamilton 1986?  
16 MR. FROST: Can you raise  
17 the sheet?  
18 MR. SMITH: Yeah.  
19 MR. FROST: Thanks.  
20 MR. SMITH: Sure.  
21 BY MR. SMITH:  
22 Q. What about Hamilton 1986?  
23 Have you looked at that, and does that  
24 form the basis of your opinion about

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1 what "communication" means.  
2 Certainly the genital tract is not  
3 an open system.  
4 BY MR. SMITH:  
5 Q. You don't believe the female  
6 genital tract is an open system?  
7 A. I believe that it's -- it's  
8 not open to the environment, that there  
9 are a variety of protective mechanisms,  
10 beginning with the external perineal skin  
11 and other mechanisms such as the labia,  
12 and clearance mechanisms through normal  
13 clearance of the tract.  
14 Q. "The case of migration of  
15 particulate material from the vagina to  
16 the peritoneal cavity has been  
17 established."  
18 Do you agree or disagree  
19 with that quote from Hamilton?  
20 MR. FROST: Objection.  
21 THE WITNESS: From the  
22 vagina, I would have to go back  
23 and look. But there have been  
24 studies that have introduced

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<p style="text-align: right;">Page 342</p> <p>1 material into the vagina, 2 particularly in animals that are 3 manipulated. 4 And I think that's what 5 they're talking about here. 6 BY MR. SMITH: 7 Q. So do you believe that if 8 talc is placed into the vagina, that it 9 then can transmigrate through the female 10 genital tract to the ovary? 11 MR. FROST: Objection. 12 THE WITNESS: I have not 13 seen those studies, no. 14 BY MR. SMITH: 15 Q. You haven't seen -- 16 A. Particulate matter. 17 Q. You haven't seen any of the 18 inert particle studies that show any of 19 that testing like -- 20 A. There is one study, I 21 believe, in the 1980s that looks at this 22 in women in a supine position. But these 23 studies that have been done, for example, 24 in rabbits and in monkeys argue against</p>	<p style="text-align: right;">Page 344</p> <p>1 A. It says that retrograde 2 migration was not considered to be 3 plausible by the group, yes. There is a 4 statement on that in the IARC monograph. 5 Q. Okay. Are you familiar with 6 the Phillip's rabbit study that found 7 talc can migrate to the fallopian tubes? 8 Phillips. 9 A. I believe that was one where 10 it was -- it wasn't perineal application. 11 I do remember that study. And it was -- 12 it may have been vaginal or applied 13 directly to the ovary. I'm not certain. 14 There was an earlier study. 15 Q. Is this in your reference 16 materials? I don't see it? 17 A. No, it's in the IARC. Well, 18 I reference the IARC monograph that has a 19 lot of references. And I believe that 20 Phillips is in that one. 21 Q. The Hamilton, last quote, 22 "The rhythmic muscular contractions of 23 the uterus that can occur spontaneous and 24 the elicit current's established" --</p>
<p style="text-align: right;">Page 343</p> <p>1 vaginal or perineal migration of talc to 2 the ovaries. 3 Q. I'm talking about if the 4 talc is placed inside the woman's vagina. 5 I'm not talking about from perineal 6 dusting. And my question is, are you of 7 the opinion that that talc, if placed in 8 the vagina of a woman, can transmigrate 9 to the fallopian tubes in a woman? 10 MR. FROST: Objection. 11 THE WITNESS: My statements 12 would be the same as the IARC 13 concludes on this. And that is, 14 that there's no evidence that this 15 happens in healthy women. That 16 what has been done in terms of the 17 experimental studies have been 18 shown in women with clearance 19 mechanisms that are compromised by 20 infection or other pathologies. 21 BY MR. SMITH: 22 Q. You're saying that IARC, the 23 2010 IARC monograph, says that 24 transmigration does not happen?</p>	<p style="text-align: right;">Page 345</p> <p>1 "established by the epithelial cells of 2 the genital tract may contribute to the 3 translocation process." 4 Do you agree or disagree 5 with that statement? 6 MR. FROST: Objection. 7 THE WITNESS: In normal 8 individuals, this would not be a 9 plausible mechanism. 10 BY MR. SMITH: 11 Q. Are you familiar with the 12 Kuntz studies about the peristolic pump? 13 A. These are the ones where I 14 believe they looked at -- or labeled 15 spermatozoa or other particles. And I 16 know they were discounted by the IARC 17 because of the experimental flaws. 18 Q. I didn't see -- do you have 19 Dr. Cramer and Dr. Godleski's 2007 case 20 study on a woman who was a chronic -- or 21 a long-time genital talc user and their 22 findings of translocation? Have you 23 looked at that article? 24 A. Is it -- if this is a case</p>

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<p>1 report I wouldn't have localized it with 2 my searches, no. 3 Q. Okay. I'm going to mark 4 what's the next exhibit, Number 33. 5 (Document marked for 6 identification as Exhibit 7 Mossman-33.) 8 BY MR. SMITH: 9 Q. And this is entitled, 10 "Correlative polarizing light and 11 scanning electron microscopy for the 12 assessment of talc in pelvic region" -- 13 "region lymph nodes." Sandra McDonald is 14 the lead author. 15 Have you seen this 16 article -- or study, excuse me? 17 A. I believe I have seen it at 18 some point in the past, yes. 19 Q. It's not in your materials 20 or your updated reference materials? 21 A. No. Mainly because these 22 are in pelvic lymph nodes, not in the 23 ovary. So I would not have included this 24 as compelling evidence one way or</p>	<p>1 THE WITNESS: No, but I'm 2 talking about the relevance. This 3 is looking at talc in lymph nodes. 4 I suggest you look at studies by 5 Dodson, et cetera, that have 6 looked and found particles of all 7 different types, including talc, 8 in lymph nodes all over the body 9 in the general population. 10 BY MR. SMITH: 11 Q. Well, then how did it get 12 there? 13 A. I told you that lymph nodes 14 are a flow system that collect -- they 15 are essentially garbage cans for inhaled 16 materials or materials in general. 17 Q. I agree. My question to you 18 is if talc, and you agree they have been 19 found in lymph nodes, they either got 20 there through inhalation or ingestion or 21 through some other route such as a 22 genital -- genital route. 23 How did it get -- how did 24 talc, in your opinion, get to lymph nodes</p>
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<p>1 another. It's been shown by others that 2 any types of particles accumulate in 3 lymph nodes all over the body. It's a 4 normal mechanism of clearance. So I 5 would not give this any relevance, 6 certainly not to the development of 7 ovarian cancers. 8 Q. So have you read this 9 article and -- and what it discusses 10 about transmigration of particles in 11 the -- in the female genital tract? 12 A. No, I have not. 13 Q. And was this in reliance of 14 your materials in forming the basis for 15 your opinion about transmigration in this 16 case? 17 A. No, it would not be relevant 18 to ovarian cancers as talc has been found 19 in lymph nodes all over the body in the 20 normal population. 21 Q. Well, that's not it's -- 22 that's not what it's discussing in this 23 paper. 24 MR. FROST: Objection.</p>	<p>1 inside human beings if it wasn't by one 2 of those routes? 3 A. It -- 4 MR. FROST: Objection. 5 THE WITNESS: It would be 6 primarily by inhalation. We know 7 that. And ingestion. Talc is in 8 a lot of different food processes. 9 It's in plastics. We're all 10 exposed to it. 11 BY MR. SMITH: 12 Q. Have you ever read the FDA's 13 response to citizen's petition on talc? 14 A. No. That -- I never would 15 have found that in the scientific 16 literature. 17 Q. It says, "While there exists 18 no direct proof of talc and ovarian 19 carcinogenesis, the potential for 20 particulates to migrate from the perineum 21 and vagina to the peritoneal cavity is 22 indisputable." 23 Do you agree or disagree 24 with that?</p>

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<p>1 MR. FROST: Objection. 2 THE WITNESS: I would assume 3 that this report is -- or letter 4 is from an individual. Certainly 5 no balanced committee would make 6 that statement. 7 BY MR. SMITH: 8 Q. Okay. "It is, therefore, 9 plausible that perineal talc and other 10 particulate that reaches the endometrial 11 cavity, fallopian tubes and ovaries may 12 elicit a foreign body-type reaction and 13 inflammatory that" -- "response that in 14 some exposed women may progress to 15 epithelial ovarian cancers." 16 Do you agree or disagree 17 with that statement? 18 MR. FROST: Objection. 19 THE WITNESS: I think it's 20 hypotheses. It's unproven and I'm 21 sure a committee would not have 22 made that statement. 23 BY MR. SMITH: 24 Q. I want to talk about your</p>	<p>1 quantitating exposure of different 2 materials to cells and culture, is based 3 on their surface area determinations 4 because it's the surface area that 5 governs their interaction with the cell 6 surface. 7 Q. Okay. And you did a 8 conversion, did you not? It's -- do you 9 have the Hillegass study by any chance? 10 Probably not. Let me grab it for you. 11 MR. FROST: Do you have one? 12 MR. SMITH: Yeah, I got it. 13 (Document marked for 14 identification as Exhibit 15 Mossman-34.) 16 BY MR. SMITH: 17 Q. I notice one of the comments 18 to -- and let's go to that right now. I 19 have got that over here. Now we might be 20 branching out to this guy here. I don't 21 know. 22 If we look at the front of 23 the second page. It says -- this is 24 reviewers to the study. Do you see that,</p>
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<p>1 Shukla study. Is that okay? 2 A. Sure. 3 Q. Do you -- you don't -- do 4 you have a copy of it? 5 MR. FROST: Yeah, I was 6 going to say we don't have a copy. 7 MR. SMITH: Yeah. Hold on. 8 (Whereupon, a discussion was 9 held off the record.) 10 BY MR. SMITH: 11 Q. Okay. Why did you use the 12 concentrations that you did in this 13 study, or why did y'all? 14 A. Okay. So we were -- we were 15 interested in the study in comparing 16 various materials or particles, fibers, 17 at equal surface area concentrations. 18 And we also expressed the data as equal 19 weight concentrations. So that we 20 compare it historically to concentrations 21 of materials used by others in other 22 studies. 23 So it's been shown that the 24 best method of dosimetry, that is, of</p>	<p>1 Doctor? This is what you provided to me. 2 A. Right. Okay. 3 Q. Okay. I'm going to attach 4 that -- excuse me. Hold on. I'm going 5 to attach that as exhibit -- let's attach 6 Shukla as Exhibit 34. 7 (Document marked for 8 identification as Exhibit 9 Mossman-35.) 10 MR. SMITH: Let's do 11 Hillegass as 35. And then this 12 collective exhibit of reviewer 13 comments with the cover letters, 14 it's May 8, 2009, University of 15 Vermont, with Jedd Hillegass on 16 the bottom. 17 (Document marked for 18 identification as Exhibit 19 Mossman-36.) 20 BY MR. SMITH: 21 Q. And this is from a reviewer. 22 Methods, Page 6. "The dose of minerals 23 expressed as surface-based concentration 24 may not be intuitive to all readers. As</p>

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<p style="text-align: right;">Page 354</p> <p>1 in the recent publication, Shukla, it 2 would be helpful if some information is 3 provided about the surface area of the 4 various minerals tested, as well as how 5 this translates into micrograms per 6 centimeter squared," right? 7 A. Yes. 8 Q. And then your response or 9 y'all's response was, "Additional 10 information regarding the surface area of 11 particulates used in these studies was 12 added to the methods section along with 13 how many micrograms squared per 14 centimeter squared translates into 15 micrograms per centimeter squared." 16 Right? 17 A. Okay. So I'm trying to 18 figure out whether this is with regard to 19 the Hillegass study; is that correct? 20 Q. Correct. 21 A. Okay. 22 Q. All right. This is my 23 question. 24 A. Sure.</p>	<p style="text-align: right;">Page 356</p> <p>1 Q. If I'm looking at asbestos 2 below at 15 micrometers squared per 3 centimeter squared, how many -- what 4 would that translate to to micrograms per 5 centimeter squared? 6 A. Micrograms, it would -- 7 Okay. So that would equal one. 8 Q. 15 would be one, right? 9 A. With asbestos. 10 Q. Right. And 75 would be -- 11 A. 75 would be five. 12 Q. Five, okay. 13 A. And 15 would be 14 approximately -- well, it's 16.2, would 15 be one with talc. And it would be, again 16 in the same range, 75 versus 81 talc. 17 So we're actually adding 18 talc at higher surface concentrations but 19 fractionally so, as compared to asbestos. 20 Q. My question is, would the 15 21 micrometers squared per centimeter 22 squared for talc that you used the 23 concentration of in this case, would that 24 equal one microgram per centimeter</p>
<p style="text-align: right;">Page 355</p> <p>1 Q. The concentrations that you 2 used, that being -- and I'm talking about 3 Shukla. I'm talking about 34 -- 4 15 micrometers squared per centimeter 5 squared and 75 micrometers squared per 6 centimeter squared, would translate to 7 what micrograms per centimeter squared? 8 A. Okay. And that's -- if you 9 look at Figure 2 in Shukla, Page 4 of 10. 10 Q. Yep. 11 A. And the top panel, you'll 12 see the vertical and the horizontal. And 13 if we look at asbestos and talc, you can 14 see here that the upper column, going 15 from 015 and from talc 15, et cetera, 16 that is the comparative weight per -- so 17 it's weight per unit area of dish. 18 So that's your weight 19 concentration. 20 The numbers below are your 21 surface area concentrations. 22 Q. Okay. So let's get on the 23 same page. 24 A. Mm-hmm.</p>	<p style="text-align: right;">Page 357</p> <p>1 squared? 2 A. Approximately, yes. 3 Q. Okay. That's what I 4 thought. 5 A. Yes. They're comparable. 6 Q. Okay. And 75 micrograms per 7 centimeter squared -- micrograms squared 8 per centimeter squared would equal five 9 micrograms per centimeter squared, right? 10 A. Yes. 11 Q. Okay. Now I'm on the same 12 page. That's what I needed. 13 A. Okay. 14 Q. All right. And do you 15 believe that those concentrations are 16 appropriate to use in in vitro studies to 17 determine the pathogenicity of minerals 18 such as talc and asbestos? 19 A. Yes. And that's based upon 20 the toxicity data that is provided in A 21 and B. So they're comparable 22 concentrations. The asbestos as we can 23 see at five, was toxic and the talc was 24 not. So we -- and you can see that in</p>



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<p>1 the dose-response that we did with five 2 concentrations of talc ranging from one 3 to 20. 4 Q. Okay. So talc you tested at 5 one microgram per centimeter squared, 6 five micrograms per centimeter squared, 7 ten micrograms per centimeter squared, 8 and 20 microgram per centimeter squared? 9 A. 15 and 20. 10 Q. 10, 15, and 20? 11 A. Yes. 12 Q. Okay. 13 A. So the message is that you 14 don't want to work with something that's 15 going to kill all the cells, so you can't 16 go higher. And in fact, that's a reason 17 that with time, we didn't look at the 18 higher concentration of asbestos. 19 Q. I want to attach this as 20 Exhibit 27 so I won't forget this. 21 Because I could. 22 (Document marked for 23 identification as Exhibit 24 Mossman-37.)</p>	<p>1 A. They only sponsored a very 2 small fraction of the studies that were 3 done with the talc. The other materials 4 and the other work was supported by a 5 grant from the National Institutes of 6 Health. 7 Q. Is it unusual to give 8 progress reports to those who sponsor 9 research? 10 A. No. It's demanded from NIH, 11 for example. In other -- in our 12 institution it is. 13 Q. It is -- is it -- it is not 14 unusual to submit proposal to industry 15 involved in regulatory and/or litigation 16 issues, correct? 17 A. Could you say that again. 18 MR. FROST: Objection. 19 BY MR. SMITH: 20 Q. Sure. It is not unusual to 21 submit proposals to industry involved in 22 regulatory and/or litigation issues? 23 MR. FROST: Objection. 24 BY MR. SMITH:</p>
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<p>1 BY MR. SMITH: 2 Q. Here we are, Shukla, 3 "Appropriate Concentration Levels to 4 Determine Pathogenicity of Asbestos and 5 Talc." And this study used concentration 6 levels of talc, at one, five, 10, 15, 7 20 micrograms per centimeter squared, 8 correct? 9 A. Yes. 10 MR. SMITH: Okay. That's 11 Exhibit 37. 12 BY MR. SMITH: 13 Q. Okay. You provided, as we 14 discussed, progress reports to the IMA 15 during the course of this study; is that 16 correct? 17 A. After a year, yes. We 18 didn't provide them with progress 19 reports. I wrote them e-mails that the 20 asbestos data was positive, but the other 21 data didn't appear to be with regard to 22 the other materials. 23 Q. And they sponsored the 24 study, correct, along with EUROTALC?</p>	<p>1 Q. Is that unusual to submit 2 proposals to industry that might be 3 involved in regulatory and/or litigation 4 issues? 5 A. To my knowledge, these 6 institutions were not involved in 7 litigation in 2005. All this work was 8 done prior to litigation ensuing in this 9 country. 10 Q. No, no, I'm just talking in 11 general. I'm not talking about 12 specifically this case. I'm not talking 13 about talc litigation. I'm not talking 14 about any particular litigation. 15 A. Fine. 16 Q. I'm just talking in general 17 terms, it is not unusual to submit 18 proposals to industry involved -- that 19 may be involved in regulatory and/or 20 litigation issues, is it? 21 MR. FROST: Objection. 22 THE WITNESS: It is not 23 unusual in toxicology to submit 24 proposals to industry as that is</p>

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<p>1 where most toxicologists reside.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. And conflicts of interest,</p> <p>4 as far as being expert witness,</p> <p>5 disclosures are up to the specific</p> <p>6 journal, correct?</p> <p>7 A. Yes.</p> <p>8 Q. Okay.</p> <p>9 A. Yes.</p> <p>10 Q. And what do you think the</p> <p>11 study shows regarding talc -- talc's</p> <p>12 carcinogenicity?</p> <p>13 MR. FROST: Objection.</p> <p>14 THE WITNESS: We weren't</p> <p>15 attempting to show changes with</p> <p>16 talc carcinogenicity.</p> <p>17 Let me emphasize that our</p> <p>18 intent in these studies and the</p> <p>19 focus was on asbestos, on</p> <p>20 crocidolite asbestos, what gene</p> <p>21 changes it induced in primarily</p> <p>22 mesothelial cells, as we didn't</p> <p>23 get any striking results in</p> <p>24 ovarian epithelial cells.</p>	<p>1 was unaware of their involvement.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Would you agree that the</p> <p>4 Shukla study showed that the</p> <p>5 non-pathogenic minerals, glass beads, and</p> <p>6 fine titanium dioxide treatment to cells</p> <p>7 resulted in no gene changes, and</p> <p>8 crocidolite asbestos caused the maximum</p> <p>9 number of gene changes followed by talc?</p> <p>10 A. No, I couldn't say that</p> <p>11 statistically. Based on the statistical</p> <p>12 assays that were performed here, as well</p> <p>13 as in the Hillegass paper, showed that</p> <p>14 the magnitude and the types of gene</p> <p>15 changes were different with talc and</p> <p>16 asbestos, but talc was comparable in</p> <p>17 numbers and types of changes to glass</p> <p>18 beads and titanium dioxide.</p> <p>19 Q. You told me that you did not</p> <p>20 study talc in the Hillegass study.</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: I didn't</p> <p>23 say --</p> <p>24 BY MR. SMITH:</p>
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<p>1 And talc was just one of</p> <p>2 other materials that were used to</p> <p>3 see whether our effects were</p> <p>4 specific to a pathogenic mineral</p> <p>5 type or induced by other materials</p> <p>6 as well. And so we used three</p> <p>7 different controls, including talc</p> <p>8 in these studies.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. You're saying talc was used</p> <p>11 as a control?</p> <p>12 A. It turned out to be a</p> <p>13 control, yes. We used it as a control of</p> <p>14 a mineral that was not associated with</p> <p>15 the development of mesothelioma as was</p> <p>16 crocidolite asbestos.</p> <p>17 Q. But at that time, it was</p> <p>18 associated with the possibility of</p> <p>19 increasing the risk in causing ovarian</p> <p>20 cancer, according to IARC, correct?</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: No. These</p> <p>23 studies were done in 2005. If</p> <p>24 IARC was involved at that point, I</p>	<p>1 Q. It wasn't tested, talc was</p> <p>2 not tested in the Hillegass study.</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: Talc is in the</p> <p>5 data. I'm sorry.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. I understand that, but you</p> <p>8 did not perform all of the tests that you</p> <p>9 did for asbestos. You did not -- you did</p> <p>10 not -- the utilization of gene profiling</p> <p>11 and proteomics to determine mineral</p> <p>12 pathogenicity in a human mesothelial cell</p> <p>13 line. You did not do gene profiling and</p> <p>14 proteomics on talc.</p> <p>15 A. We did. And we had looked</p> <p>16 at it -- we did it in the Shukla study,</p> <p>17 and we looked at the microarray data by</p> <p>18 something called principle component</p> <p>19 analysis in the Hillegass study and</p> <p>20 showed that the changes with talc were</p> <p>21 different in the two different cell</p> <p>22 types, and they were different in</p> <p>23 magnitude and types of gene changes from</p> <p>24 asbestos, and that's in the first figure</p>

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<p>1 in the Hillegass study.</p> <p>2 Q. Oh, we'll -- we'll get to</p> <p>3 the Hillegass study in a minute.</p> <p>4 A. Okay.</p> <p>5 Q. Let's -- let's stick with</p> <p>6 Shukla. All right. I marked -- I marked</p> <p>7 the next -- well, I'm going to mark the</p> <p>8 next exhibit as 38.</p> <p>9 (Document marked for</p> <p>10 identification as Exhibit</p> <p>11 Mossman-38.)</p> <p>12 BY MR. SMITH:</p> <p>13 Q. And this on the NCBI, which</p> <p>14 is the public access of studies, and it</p> <p>15 says status public on September 19, 2011,</p> <p>16 "Alterations in gene expression in human</p> <p>17 mesothelial cells, correlate with mineral</p> <p>18 pathogenicity, organisms, homo sapiens,"</p> <p>19 this is your study we are talking about,</p> <p>20 the Shukla, correct?</p> <p>21 A. It is. Yes.</p> <p>22 Q. Okay. And this is just a</p> <p>23 publication -- a public publication of</p> <p>24 this study, of the summary and overall</p>	<p>1 dioxide treatment to cell resulted in no</p> <p>2 gene changes, crocidolite asbestos caused</p> <p>3 the maximum number of gene changes</p> <p>4 followed by talc."</p> <p>5 And you told me that that</p> <p>6 study, Shukla, did not state that.</p> <p>7 Why would Jeffrey Bond state</p> <p>8 that in the overall design in this</p> <p>9 publication released to the public if</p> <p>10 you're saying the study doesn't reveal</p> <p>11 that in Shukla?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Yeah. We</p> <p>14 looked at the statistics which are</p> <p>15 not referenced here. And I'm not</p> <p>16 sure why he would have put -- not</p> <p>17 included the statistics.</p> <p>18 But it's important to note</p> <p>19 that the statistical changes by</p> <p>20 talc were not significantly</p> <p>21 elevated as compared to the</p> <p>22 controls which were titanium</p> <p>23 dioxide and glass beads.</p> <p>24 And that was certainly the</p>
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<p>1 design and contributors and citations.</p> <p>2 And I want to look at the overall design.</p> <p>3 But let me ask you first.</p> <p>4 Who is Jeffrey Bond?</p> <p>5 A. Jeffrey Bond is director of</p> <p>6 the biostatistics department within our</p> <p>7 cancer center at the University of</p> <p>8 Vermont. So he was the one who did the</p> <p>9 statistics on these studies.</p> <p>10 Q. And if you look at the</p> <p>11 second page, he's listed as the contact</p> <p>12 name. It says, "Organization, University</p> <p>13 of Vermont; department, microbiology and</p> <p>14 molecular genetics."</p> <p>15 Do you see that, in</p> <p>16 Burlington, Vermont?</p> <p>17 A. Yes.</p> <p>18 Q. And it says, "Overall</p> <p>19 design" -- it says, "Summary," and then</p> <p>20 it says, "Overall design."</p> <p>21 In the last sentence of</p> <p>22 overall design of this study, the Shukla</p> <p>23 study, it says, "While nonpathogenic</p> <p>24 minerals, glass beads and fine titanium</p>	<p>1 case following up with even more</p> <p>2 sophisticated assays in the</p> <p>3 Hillegass paper.</p> <p>4 BY MR. SMITH:</p> <p>5 Q. But you did not look at</p> <p>6 talc, the higher concentrations, at</p> <p>7 24 hours to determine if it was dose</p> <p>8 dependent just like asbestos.</p> <p>9 MR. FROST: Objection to</p> <p>10 form.</p> <p>11 THE WITNESS: You are wrong.</p> <p>12 We looked at eight hours at a low</p> <p>13 and high concentration of talc.</p> <p>14 It certainly was dose dependent.</p> <p>15 We found only one gene at the</p> <p>16 lower concentrations, and 30 at</p> <p>17 the highest.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. Okay.</p> <p>20 A. When we took out the</p> <p>21 experiment to 24 hours at low</p> <p>22 concentrations of both materials, we saw</p> <p>23 that changes with asbestos increased and</p> <p>24 the talc at the lowest concentration did</p>

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<p style="text-align: right;">Page 370</p> <p>1 not result in a higher number.  2 So we certainly did do  3 dose-response experiments.  4 Q. Point me into the Shukla  5 study where you tested talc at the higher  6 concentration on peritoneal mesothelial  7 cells at 24 hours.  8 MR. FROST: Objection.  9 THE WITNESS: I'm saying we  10 didn't look at 24 hours --  11 BY MR. SMITH:  12 Q. Thank you.  13 A. -- because our cells were  14 dead.  15 Q. Where does that state there?  16 Where is it stated?  17 A. Where? In the paper?  18 Q. That the cells were dead.  19 A. All you have to do is look  20 at the asbestos results --  21 Q. No, ma'am. I'm talking  22 about for talc.  23 A. We -- we wouldn't have  24 looked -- we wouldn't have looked at talc</p>	<p style="text-align: right;">Page 372</p> <p>1 did cause an increase.  2 MR. SMITH: Again, I'm going  3 to object as nonresponsiveness.  4 BY MR. SMITH:  5 Q. My question is simple and  6 it's easy and clean and neat.  7 Point me to where in the  8 paper at high -- the higher  9 concentration, that you exposed talc to  10 peritoneal mesothelial cells that you say  11 line the fallopian tubes, ovaries and  12 peritoneal cavity at 24 hours. Tell me  13 where you did that.  14 MR. FROST: Objection.  15 THE WITNESS: Let's go  16 back --  17 BY MR. SMITH:  18 Q. No, ma'am. I need an answer  19 to the question. Did -- tell me in the  20 paper. Show it to me.  21 Where did you expose at  22 24 hours --  23 A. Why --  24 Q. Ma'am, let me finish my</p>
<p style="text-align: right;">Page 371</p> <p>1 without looking at asbestos. Our focus  2 was on asbestos. Why would I look at  3 talc when I couldn't compare it to  4 asbestos?  5 Q. Because I don't have a  6 problem with you making assumptions about  7 asbestos in this paper. The problem I've  8 got is you making assumptions that --  9 that deal with ovarian issues and ovarian  10 gene expression changes, and what this  11 study says about exposure of talc to  12 peritoneal mesothelial cells.  13 And my question is this:  14 Did you test talc at the higher  15 concentration with peritoneal mesothelial  16 cells at 24 hours, yes or no?  17 MR. FROST: Objection.  18 THE WITNESS: We did not.  19 We looked at the low  20 concentrations of both asbestos  21 and talc at comparable  22 concentrations and showed that  23 talc changes did not increase over  24 time, but asbestos concentrations</p>	<p style="text-align: right;">Page 373</p> <p>1 question. I'm just going to ask a  2 question.  3 Where -- point me in the  4 paper where you exposed peritoneal  5 mesothelial cells to talc at the higher  6 concentrations at 24 hours, point it to  7 me.  8 MR. FROST: Objection.  9 THE WITNESS: We -- we did  10 not look at asbestos or talc at  11 24 hours at the higher  12 concentrations because the cells  13 were dying from asbestos. That's  14 why.  15 BY MR. SMITH:  16 Q. But you don't know if they  17 would have died from talc at 24 hours?  18 MR. FROST: Objection.  19 THE WITNESS: It wouldn't  20 have made any difference.  21 BY MR. SMITH:  22 Q. Sure it would have, because  23 then we could sit here and say, regarding  24 ovarian cells -- peritoneal --</p>

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<p style="text-align: right;">Page 374</p> <p>1 peritoneal -- excuse me, peritoneal 2 mesothelial cells that line the ovary and 3 fallopian tubes and peritoneal cavity, 4 whether there was a dose-dependent 5 reaction because you saw 30 genes changes 6 at eight hours. And if the gene 7 expression would have gone up at 24, then 8 we could say there was a dose-dependent 9 reaction there? 10 MR. FROST: Objection. 11 THE WITNESS: No. I want to 12 emphasize that we looked at two 13 concentrations of talc and 14 asbestos at eight hours and there 15 was a dose-dependent change with 16 asbestos that was of a huge 17 magnitude. 18 That was not the case with 19 talc. And the results were 20 essentially the same as we got 21 with the other control particles. 22 BY MR. SMITH: 23 Q. Okay. Well, tell me -- show 24 me in this paper where -- I don't see the</p>	<p style="text-align: right;">Page 376</p> <p>1 beads. 2 BY MR. SMITH: 3 Q. Well, hold on. Show me. If 4 you're going to -- if you're going to 5 make general statements like that about 6 this study, I have charts. I can look at 7 them. I can look at the 30 genes that 8 were changed and altered at eight hours 9 at the higher concentrations of 10 peritoneal mesothelial cells by talc. 11 You're now making a 12 statement that I don't see anywhere in 13 this paper that titanium dioxide and 14 glass beads did had similar gene changes 15 and acted in a similar way that talc did 16 compared to mesothelial cells at this 17 concentration at these hours. 18 And my question is, where is 19 that table? 20 MR. FROST: Objection. 21 THE WITNESS: Of controlled 22 gene changes? There weren't any 23 significant gene changes. 24 BY MR. SMITH:</p>
<p style="text-align: right;">Page 375</p> <p>1 chart for all the genes -- all the genes 2 altered by the exposure to titanium 3 dioxide and glass beads. 4 A. They were -- 5 Q. I see a chart for all the 6 genes altered by crocidolite asbestos to 7 peritoneal mesothelial cells. I see the 8 table of non-fibrous talc to peritoneal 9 mesothelial cells and 30 genes change. 10 I need -- where is -- show 11 me where the chart is that titanium 12 dioxide and glass beads changed the 13 comparable amount of genes that talc 14 compared to mesothelial cells at higher 15 concentrations -- 16 MR. FROST: Objection. 17 THE WITNESS: They didn't 18 cause any increases in more than 19 twofold of -- and if you look at 20 the data with talc, even with the 21 30, we're talking about looking at 22 thousands of genes. That number 23 statistically is as low as the 24 titanium dioxide or the glass</p>	<p style="text-align: right;">Page 377</p> <p>1 Q. Thank you. Thank you. 2 And -- 3 A. That is my point. 4 Q. Okay. And let's look at 5 Hillegass. 6 A. Okay. 7 Q. Number 35. You have 8 chrysotile asbestos, which you would 9 agree with me is carcinogenic, correct? 10 A. I didn't use chrysotile 11 asbestos in these studies. 12 Q. My question to you, is 13 chrysotile asbestos carcinogenic? 14 MR. FROST: Objection. 15 THE WITNESS: I think we 16 went through this previously. But 17 if you talk about mesothelioma, 18 there's a debate on whether the 19 risk is zero or one or a low 20 number. 21 BY MR. SMITH: 22 Q. Does IARC and the National 23 Toxicology Program consider all types of 24 asbestos, including chrysotile, human</p>



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<p style="text-align: right;">Page 378</p> <p>1 carcinogens?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: And that's</p> <p>4 based on lung cancers and</p> <p>5 mesothelioma. And yes, they do.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Okay. Here, seven</p> <p>8 micrograms per centimeter squared, do you</p> <p>9 see that, Doctor? Of chrysotile. This</p> <p>10 is on your Table 3 of another study,</p> <p>11 correct?</p> <p>12 A. Okay. You are going to have</p> <p>13 to tell me what page that's on.</p> <p>14 Q. It's 18 of 18.</p> <p>15 A. Okay. Okay. This is a</p> <p>16 summary of work done by others in</p> <p>17 comparison to our work.</p> <p>18 Q. Okay. And in the Shukla</p> <p>19 study the higher concentration is</p> <p>20 75 micrometers squared per centimeter</p> <p>21 squared would be five micrograms per</p> <p>22 centimeter squared, correct?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. So the concentration</p>	<p style="text-align: right;">Page 380</p> <p>1 Therefore, we just talked</p> <p>2 about the concentration that you used in</p> <p>3 Shukla of talc would be five micrograms</p> <p>4 per centimeter squared or a lower</p> <p>5 concentration than is used for chrysotile</p> <p>6 on this chart, correct?</p> <p>7 MR. FROST: Objection.</p> <p>8 THE WITNESS: Yeah. I'm not</p> <p>9 sure what you're getting at here.</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Well --</p> <p>12 A. Let me just double-check</p> <p>13 what you're saying, because I'm not sure</p> <p>14 it makes sense.</p> <p>15 Q. We've been through this in</p> <p>16 Brower.</p> <p>17 A. That's what I'm reiterating.</p> <p>18 It didn't make sense either then. Okay.</p> <p>19 Q. Well, let's just agree on</p> <p>20 fundamentals. I mean, it's pretty easy.</p> <p>21 The higher concentration of five -- 75</p> <p>22 micrometers per centimeter squared that</p> <p>23 you used in Shukla for talc equals five</p> <p>24 micrograms per centimeter squared,</p>
<p style="text-align: right;">Page 379</p> <p>1 that you used of talc in Shukla is lower</p> <p>2 than the concentration here of</p> <p>3 chrysotile, seven micrograms per</p> <p>4 centimeter squared. And the results of</p> <p>5 the study as far as genes altered at four</p> <p>6 hours were eight by chrysotile, correct?</p> <p>7 A. Yes.</p> <p>8 Q. And at eight hours in talc</p> <p>9 at a lower concentration, how many genes</p> <p>10 were upregulated?</p> <p>11 A. In our studies?</p> <p>12 Q. Yes.</p> <p>13 A. One gene was the ATF3 --</p> <p>14 Q. Ma'am --</p> <p>15 A. -- at the lowest</p> <p>16 concentration.</p> <p>17 Q. Ma'am, I'm talking about --</p> <p>18 I'm talking about -- I'm talking about</p> <p>19 the concentration used at the higher</p> <p>20 concentration in your study equals five</p> <p>21 micrograms per centimeter squared. The</p> <p>22 chrysotile that's on this table is seven</p> <p>23 micrograms per centimeter squared as the</p> <p>24 concentration.</p>	<p style="text-align: right;">Page 381</p> <p>1 correct?</p> <p>2 A. In talc, the concentration</p> <p>3 of five micrograms per centimeter squared</p> <p>4 with talc equaled -- I'm sorry, yeah --</p> <p>5 equals 81 surface area. Okay.</p> <p>6 Q. So five micrograms per</p> <p>7 centimeter squared.</p> <p>8 A. Yes.</p> <p>9 Q. Okay. So we're looking --</p> <p>10 this study that you cite in Hillegass for</p> <p>11 chrysotile that IARC and NTP say is</p> <p>12 carcinogenic to humans, uses two</p> <p>13 micrograms per centimeter squared higher</p> <p>14 concentration than you used for talc at</p> <p>15 the higher concentration in Shukla, and</p> <p>16 eight -- excuse me -- at four hours, how</p> <p>17 many genes were altered for chrysotile?</p> <p>18 MR. FROST: Objection to</p> <p>19 form.</p> <p>20 THE WITNESS: Eight. But</p> <p>21 let me emphasize.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. No, ma'am. I don't have a</p> <p>24 question. The question I asked, and how</p>

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<p>1 many genes were upregulated by talc at a 2 lower concentration at eight hours? 30, 3 correct? 4 A. Right. So are you 5 implicating that the results here with a 6 completely different cell type are 7 relevant to what I did in human 8 mesothelial cells or ovarian epithelial 9 cells? 10 Q. Ma'am, you're trying to 11 extrapolate all your work in asbestos to 12 ovarian cancer and what talc's effect on 13 cells that have to do with ovarian 14 cancer. 15 A. I'm sorry, sir -- 16 MR. FROST: Objection. 17 THE WITNESS: -- but we have 18 not discussed ovarian epithelial 19 cells, because I got no changes 20 with talc in ovarian epithelial 21 cells. 22 BY MR. SMITH: 23 Q. Where do the large majority 24 of the ovarian cancers that we discussed</p>	<p>1 A. No one has used fallopian -- 2 normal epithelial cells in any gene 3 profiling assay. We used the most normal 4 cell type that we could get. And that 5 was the ovarian epithelial cell line from 6 Dr. Auersperg. 7 Q. You used immortalized cell 8 in your Shukla study? 9 A. I used contact-inhibited 10 immortalized cells, yes. 11 Q. Okay. And is it appropriate 12 to use immortalized cells in in vitro 13 studies to study -- study cellular 14 reactions? 15 A. It depends on what you're 16 trying to say. If you recall, our 17 emphasis here was to determine in cell 18 lines that are relevant to humans, that 19 is human cell lines, whether significant 20 gene changes were observed with 21 pathogenic mineral findings that were not 22 observed with nonpathogenic mineral 23 fibers. 24 We weren't attempting to do</p>
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<p>1 originate. And that is the serous type. 2 Nearly 90 percent of the epithelial 3 ovarian cancers in the United States, do 4 they originate in the surface of the 5 epithelium of the -- surface area of the 6 ovary or in the fallopian tubes, ma'am? 7 MR. FROST: Objection. 8 THE WITNESS: So we don't 9 know. The majority are thought 10 nowadays to originate in the 11 fallopian tubes. That has no 12 bearing upon our results at all. 13 BY MR. SMITH: 14 Q. I totally agree your results 15 have no bearing on that. 16 MR. FROST: Objection. 17 THE WITNESS: Well, you 18 would like to think so. But the 19 fact remains that we got no 20 changes with talc in ovarian 21 epithelial cells. 22 BY MR. SMITH: 23 Q. Did you use fallopian tube 24 cells in Shukla?</p>	<p>1 transformation. We were attempting to 2 look and see whether minerals at a 3 variety of different comparable surface 4 areas and weight concentrations induced 5 the same responses, and they don't. 6 Talc is inert as is glass 7 beads and titanium dioxide. 8 Q. Inert. What is your 9 definition of inert? 10 A. The same as -- it -- it's 11 uncharged. It's inert in terms of cell 12 reactions. 13 Look at the toxicity data 14 for talc, for example. You have to go 15 extremely high to get a toxic amount. 16 And I would use inert as did IARC 17 repeatedly. 18 Q. So you're saying -- you're 19 saying that talc -- wait. Did you use 20 cosmetic-grade talc or industrial grade 21 talc for Shukla? 22 MR. FROST: Objection. 23 THE WITNESS: You know, I 24 stated that several times. I</p>

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<p style="text-align: right;">Page 386</p> <p>1 think we know the answer.  2 BY MR. SMITH:  3 Q. Okay. You're saying that  4 talc is inert when at 75 micrometers  5 squared per centimeter squared at eight  6 hours, it showed 30 alterations of gene  7 expressions?  8 A. Let's look at our ratio of  9 30 over 3,000 compared to 1 over 3,000.  10 And the 30 --  11 Q. What -- what comparison are  12 you making that from?  13 MR. FROST: Objection.  14 THE WITNESS: I'm talking  15 about the inert materials that I  16 used. The glass beads --  17 BY MR. SMITH:  18 Q. Where is that -- where is --  19 again I'm going to go back to it.  20 If you're going to say,  21 because it's not written in this study  22 anywhere what you just said.  23 What -- what you just said,  24 that talc is inert just like glass beads</p>	<p style="text-align: right;">Page 388</p> <p>1 is the chart in the study that shows me  2 that titanium dioxide and glass beads  3 altered 30 genes at eight hours at  4 75 micrometers squared per centimeter  5 squared in peritoneal mesothelial cells?  6 Show me the chart.  7 MR. FROST: Objection.  8 THE WITNESS: They didn't  9 alter any genes that were elevated  10 above two to three, and the 30  11 that were elevated by talc, which  12 were not seen at a low  13 concentration, were statistically  14 of the same magnitude as what was  15 seen with glass beads and titanium  16 dioxide.  17 And that is expanded upon in  18 the Hillegass paper.  19 BY MR. SMITH:  20 Q. We'll get to that.  21 A. Okay.  22 (Document marked for  23 identification as Exhibit  24 Mossman-39.)</p>
<p style="text-align: right;">Page 387</p> <p>1 and just like titanium dioxide --  2 A. Yes.  3 Q. -- and does -- and caused a  4 similar number of gene expression changes  5 as talc so they acted the same, which now  6 I can say they are all inert, even though  7 they changed, altered 30 genes.  8 A. That -- it's insignificant.  9 Q. Show me, show me the chart  10 of where I can go, you know what,  11 Dr. Mossman is right, I can look at this  12 chart over here, it shows gene expression  13 changes, 30 of them. And then I can go  14 over here and look at glass beads and  15 titanium dioxide, and go, wow, they acted  16 the same. Where is that?  17 MR. FROST: Objection.  18 THE WITNESS: Let's look at  19 the fraction of gene changes, and  20 we were looking at thousands of  21 gene changes.  22 So you put 30 --  23 BY MR. SMITH:  24 Q. Where is the chart? Where</p>	<p style="text-align: right;">Page 389</p> <p>1 BY MR. SMITH:  2 Q. This is Table 6. This is  3 here in your report. Do you recall that?  4 A. Right.  5 Q. Okay. I see talc. I see  6 asbestos --  7 A. Yeah.  8 Q. -- I see gene changes right  9 here at the higher concentrations. 236  10 of the most potent form of asbestos,  11 crocidolite asbestos, correct?  12 A. That's correct.  13 Q. And you told me that  14 different carcinogens can have varying  15 potencies, correct?  16 A. Different carcinogens? Talc  17 and asbestos are not different  18 carcinogens.  19 Q. In general. Different  20 carcinogens can be of different potency,  21 correct, but they are still carcinogens?  22 MR. FROST: Objection.  23 THE WITNESS: Yeah, I mean  24 that doesn't really make sense.</p>

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<p>1 Everything should have a 2 dose-response and a threshold, and 3 it's going to be different with 4 different materials. 5 BY MR. SMITH: 6 Q. All right. We'll get to 7 that in a minute in Brower, your 8 testimony. 9 A. Okay. 10 Q. All right. Hereafter, look 11 at that, 30 genes altered at -- that 12 should be -- 13 A. That's switched around. 14 You're right. 15 Q. It should be -- that's 16 wrong. It should be eight hours. 17 A. Yeah. 18 Q. Okay. I'm looking right 19 here at fine titanium dioxide and glass 20 beads and low -- and I don't see a high 21 concentration. Why -- where is the high 22 concentration to fine titanium dioxide? 23 MR. FROST: Objection. 24 THE WITNESS: Okay. So if</p>	<p>1 titanium dioxide. 2 Q. Okay. So there is no chart. 3 In fact, there's a chart in 4 your report that shows there are no genes 5 altered by fine titanium dioxide at low 6 concentrations and glass beads at high 7 concentrations, and that talc at high 8 concentrations altered 30 genes, right? 9 A. Yes. But again, I emphasize 10 that we're -- if you put that back on 11 there, we can talk about it. 12 Q. Oh, I'm sorry. 13 A. Okay. So we're looking -- 14 again, the emphasize is on asbestos, and 15 we're looking in mesothelial cells at low 16 and high concentrations at 24 hours to 17 demonstrate a dose-response. We don't -- 18 at low and high concentrations, we get 19 a -- a dose-response. The magnitude is 20 not of the same type. In fact, the 21 changes in the genes, including going up 22 and down, were not of the same type. 23 Q. Ma'am, I asked you earlier. 24 You're the one that went beyond what's</p>
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<p>1 we look at -- 2 BY MR. SMITH: 3 Q. I'm just asking where is it 4 on this chart. 5 A. Okay. At low 6 concentrations, at 24 hours, fine 7 titanium dioxide was run, and the high 8 glass beads were run at eight and 9 24 hours. 10 Q. Ma'am. 11 A. Yeah. 12 Q. Tell me how many genes are 13 altered in this chart by glass beads at 14 high concentrations. 15 A. None. 16 Q. Tell me how many genes are 17 altered by fine titanium dioxide at high 18 concentrations. 19 Was it done? 20 MR. FROST: Objection. 21 BY MR. SMITH: 22 Q. I don't see it. 23 A. It was -- it was done at the 24 low amount and not at the high amount for</p>	<p>1 in -- written down in this report and 2 told me that talc at the high 3 concentrations acted just inert just like 4 fine titanium dioxide and just like glass 5 beads -- 6 A. It -- 7 Q. And now my question to you 8 is -- 9 A. Yes. 10 Q. -- and you said they altered 11 the same amount of genes. And you 12 said -- and I said where is the chart, 13 and you kept answering your question. 14 And I -- so I went and 15 pulled the chart that you have in your 16 report. 17 A. Right. 18 Q. And we can look at how many 19 genes are altered by glass beads at the 20 high concentration, right? 21 What does it say? 22 MR. FROST: Objection. 23 THE WITNESS: Yeah, when -- 24 when one presents microarray data,</p>

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<p>1 you present significant gene 2 changes. There's no data here for 3 thousands of genes because we 4 didn't see any. We're talking 5 about bold increases. 6 BY MR. SMITH: 7 Q. That's what I'm talking 8 about. 9 A. It's got to be two or 10 greater -- 11 Q. I agree. 12 A. So what I'm telling you is 13 that with asbestos, we see low, 29, which 14 goes up to fourfold higher, eight hours. 15 With talc at low, we see an 16 insignificant amount compared to the 17 other materials we're looking, that does 18 not go up like asbestos. 19 So we see unique changes to 20 asbestos. That's what we are focusing 21 on. 22 MR. SMITH: That's not my 23 question, Doctor. I'm going to 24 object to nonresponsiveness.</p>	<p>1 A. There are no genes that are 2 increased above twofold levels. 3 Q. Thank you. 4 A. That's the zero number. 5 Q. Does talc have a zero number 6 by it at the high concentrations at 24 7 hours -- at eight hours? 8 A. 30, compared to the total 9 number of genes that we looked at, which 10 were in the thousands, the ratio of that 11 compared to the one ratio with titanium 12 dioxide or glass beads was insignificant. 13 30 genes means nothing. 14 Q. 30 genes means nothing? 15 A. That's correct. It's 16 insignificant. And that was borne out by 17 one set of analyses called ANOVA in the 18 Shukla paper and another set of analyses 19 called PCA analyses in the Hillegass. 20 Q. But you didn't do PCA 21 analysis on talc in Hillegass? 22 MR. FROST: Objection to 23 form. 24 THE WITNESS: Yes, we did.</p>
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<p>1 BY MR. SMITH: 2 Q. My question had to do -- 3 you're talking -- and stated that talc 4 was an inert substance and it did not 5 react with cells. And you said it's 6 inert just like titanium dioxide and 7 glass beads that were controls. And I 8 said what is the definition of inert? 9 A. Okay. So -- 10 Q. And you said causes cellular 11 responses. And my question to you is, 12 show me. I can see where talc at high -- 13 the higher concentration at eight hours 14 altered 30 genes. Show me on this chart 15 where glass beads or fine titanium 16 dioxide altered any. 17 MR. FROST: Objection. 18 BY MR. SMITH: 19 Q. Can you show it to me? 20 MR. FROST: Objection. 21 THE WITNESS: It's not on 22 this chart. 23 BY MR. SMITH: 24 Q. In fact, you put zero.</p>	<p>1 It's in the data. 2 BY MR. SMITH: 3 Q. Okay. We'll get there. 4 A. We went through this before. 5 Let's look at Figure 1, and the talc data 6 is graphed. 7 Q. Okay. All right. We'll go 8 through it. 9 A. Okay. 10 Q. You stated earlier in the 11 depo that minerals such as asbestos and 12 talc react differently to human cells 13 depending on the shape, size -- shape, 14 size, and crystallinity; is that correct? 15 A. Yes. 16 Q. And that you admitted that 17 shape, size, and crystallinity of 18 minerals such as asbestos and talc vary 19 from type and grade of talc and different 20 types and different mines that they're 21 mined from, right? 22 A. Yes. 23 Q. Okay. And this study did 24 not test cosmetic-grade talc, correct?</p>

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<p style="text-align: right;">Page 398</p> <p>1 MR. FROST: Objection.  2 THE WITNESS: It tested  3 industrial talc.  4 BY MR. SMITH:  5 Q. It did not test  6 cosmetic-grade talc, correct?  7 MR. FROST: Objection.  8 THE WITNESS: It did not  9 look at that directly.  10 BY MR. SMITH:  11 Q. And it did not -- therefore,  12 did not test the type of or the grade of  13 talc that's in Baby Powder or Shower to  14 Shower, correct?  15 MR. FROST: Objection.  16 THE WITNESS: The grade of  17 talc -- again, you'll have to fill  18 me in on what grade means.  19 BY MR. SMITH:  20 Q. So you don't know that the  21 grade of talc that's in Baby Powder or  22 Shower to Shower is cosmetic-grade talc?  23 A. I'm assuming it is.  24 Q. So the study did not examine</p>	<p style="text-align: right;">Page 400</p> <p>1 human fallopian tube cells?  2 A. No. Well, let me -- I want  3 to qualify that, because I'm not certain  4 where these ovarian epithelial cells came  5 from. They came from a tissue bank.  6 They were normal in terms of -- they grew  7 in anchorage-dependent conditions.  8 But I don't want to tell you  9 what their source is without looking it  10 up further.  11 Q. In Table 3 of Shukla, the  12 genes that were upregulated at  13 75 micrometers squared per centimeter  14 squared at eight hours, do you know if  15 any of those genes have been associated  16 with primary peritoneal mesotheliomas?  17 MR. FROST: Objection.  18 THE WITNESS: The -- I  19 don't. They're certainly  20 indicative of some of the pathways  21 we've followed up on. But we  22 haven't isolated these out  23 individually to study them.  24 BY MR. SMITH:</p>
<p style="text-align: right;">Page 399</p> <p>1 the type or -- the type of talc that is  2 in Baby Powder or Shower to Shower, the  3 particular grade, correct?  4 MR. FROST: Objection.  5 THE WITNESS: The source of  6 talc was a mining talc.  7 BY MR. SMITH:  8 Q. And what mine did the talc  9 used in the Shukla study come from?  10 A. It's something called  11 Barrett's Minerals. I don't know where  12 the mine is.  13 Q. I believe it's in Montana.  14 It states in the study.  15 Did the study use the talc  16 from any of the mines that J&amp;J used for  17 its Baby Powder or Shower to Shower  18 products, that being from Vermont, Italy,  19 Korea, or China?  20 MR. FROST: Objection.  21 THE WITNESS: No.  22 BY MR. SMITH:  23 Q. Okay. Have you ever  24 performed a study on talc's effect on</p>	<p style="text-align: right;">Page 401</p> <p>1 Q. So you don't know if any of  2 these genes that were upregulated in  3 Table 3 by talc are actually those genes  4 involved in the development of peritoneal  5 cancer?  6 MR. FROST: Objection.  7 THE WITNESS: That's  8 correct. I don't know about genes  9 that are upregulated in peritoneal  10 cancers.  11 MR. SMITH: Okay. I'm going  12 to attach the next numbered  13 exhibit, which would be 40.  14 (Document marked for  15 identification as Exhibit  16 Mossman-40.)  17 BY MR. SMITH:  18 Q. This is -- the lead author  19 is Dragon. Have you ever seen this  20 study? It's from 2015.  21 A. Yes.  22 Q. You have seen this?  23 A. I have.  24 Q. "Differential Susceptibility</p>

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<p>1 of Human Pleural and Peritoneal 2 Mesothelial Cells to Asbestos Exposure"? 3 A. Yes. 4 Q. It states in the abstract -- 5 actually this is from Vermont College 6 here, right, College of Medicine? 7 A. Yeah. Dr. Shukla is the 8 senior author. 9 Q. That's correct. And the 10 abstract, "Malignant mesothelioma, or MM, 11 is an aggressive cancer of mesothelial 12 cells of the pleural and peritoneal 13 cavities. In 85 percent of cases both 14 pleural and peritoneal malignant 15 mesothelioma is caused by asbestos 16 exposure. Although both are 17 asbestos-induced cancers, the incidence 18 of pleural malignant mesothelioma is 19 significantly higher at 85 percent than 20 peritoneal malignant mesothelioma at 21 15 percent." 22 And down at the bottom it 23 says, "Our results are consistent with 24 the hypothesis that differences in</p>	<p>1 mesothelioma. 2 Do you see that, the fold 3 changes? 4 A. These aren't mesothelioma 5 cells. These are two normal cell lines 6 that are normal pleural mesothelial cells 7 and a cell line including one we used in 8 our study, that were peritoneal. 9 Q. Correct. 10 A. So these are not tumors. 11 You can't say anything about -- 12 Q. That's not what I'm -- I 13 didn't mention tumor. You're the one 14 that brought up tumor. I did not say 15 that, did I? 16 A. No, you didn't, but you said 17 mesothelioma cells. 18 Q. Well, we see that IL-8, 19 CXCL2, CXCL3, IL-6, ATF3 were all 20 upregulated in pleural mesothelial cells 21 and in peritoneal mesothelial cells. 22 Do you see that? 23 A. Yes. By asbestos. 24 Q. Okay. And were those some</p>
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<p>1 incidences of pleural and peritoneal 2 malignant mesothelioma upon exposure to 3 asbestos are the result of differences in 4 mesothelial cell physiology that lead to 5 differences in the inflammatory response 6 which leads to cancer." 7 Do you see that? 8 A. I do. 9 Q. Do you agree with that? 10 MR. FROST: Objection. 11 THE WITNESS: I do with 12 regard to cancer by asbestos. 13 BY MR. SMITH: 14 Q. Okay. And if you flip to 15 Page 24. It's a chart. If you look at 16 it, Figure A is transcripts known to be 17 involved with malignant mesothelioma that 18 were significantly differential -- 19 differentially expressed in all cell 20 lines. 21 But if you look at IL-8 22 IL-6, ATF3, ATF3, the CXCL2, CXCL3, those 23 were all altered in malignant 24 mesothelioma and in peritoneal</p>	<p>1 of the same cell lines -- excuse me. 2 Were those some of the same genes, IL-8, 3 CXCL2, CXCL3, IL-6 and ATF3 that were 4 upregulated in peritoneal mesothelial 5 cells at the concentrations of eight 6 hours of talc in your study in Shukla? 7 MR. FROST: Objection. 8 THE WITNESS: Some of them, 9 certainly the ATF3 was. 10 BY MR. SMITH: 11 Q. IL-8? 12 A. IL-8, which could have many 13 functions. 14 Q. CXCL2 and CXCL3, correct? 15 A. I'd have to go back and 16 look, but they're chemokines. I believe 17 one of them might have been upregulated 18 by talc. 19 Q. IL-6? 20 A. Yeah. And this all makes 21 sense, because we know that talc induces 22 acute inflammation and antiinflammation 23 at -- by ATF3 is -- is a -- certainly a 24 protective response of the cells.</p>

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<p>1 Q. And that was -- and the 2 same -- and pleural mesothelial cells 3 were upregulated, those same genes were 4 upregulated by crocidolite asbestos that 5 we know, you admit, causes mesothelioma, 6 correct? 7 A. Are you suggesting that 8 because a gene goes up it's associated 9 with mesothelioma? 10 Q. No, I'm just saying, would 11 you agree with me that this chart shows 12 and tests crocidolite asbestos and shows 13 gene changes in pleural mesothelial 14 cells? 15 A. It shows gene changes in 16 pleural and peritoneal mesothelial 17 cells -- 18 Q. And my question -- 19 A. Yeah. 20 Q. -- my question is, would you 21 agree with me that crocidolite asbestos 22 causes malignant mesothelioma? 23 MR. FROST: Objection. 24 THE WITNESS: Yes. But</p>	<p>1 you produced documents. Do you recall 2 that? 3 A. I do. 4 Q. And -- and I'm going to 5 attach that as an Exhibit 41. 6 (Document marked for 7 identification as Exhibit 8 Mossman-41.) 9 BY MR. SMITH: 10 Q. And just show it to you. Do 11 you recall this? Affidavit of Brooke 12 Mossman you provided to me? 13 A. Yes. 14 Q. Okay. And -- and I'll show 15 you your signature at the back. 16 A. Okay. 17 Q. And that's your signature 18 you provided to me? 19 A. Yes. 20 Q. Okay. I'm going to attach 21 that as Exhibit 41. 22 And you produced some 23 documents to me. Some of -- some of 24 them -- and there were a lot -- of drafts</p>
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<p>1 that's not what we're -- we're 2 looking at here. 3 BY MR. SMITH: 4 Q. Okay. That's not what I'm 5 saying. I'm just showing, on this chart, 6 the different gene changes that by a 7 known substance to cause malignant 8 mesothelioma, right? 9 And some of the genes that 10 were changed are IL-8, CXCL2, CXCL3, 11 IL-6, ATF3. And those were the same 12 genes that were upregulated by talc at 13 the higher concentration at eight hours 14 in your Shukla paper, right? 15 MR. FROST: Objection. 16 THE WITNESS: Some of them 17 were. I would say half of the 18 genes that were significant, the 19 IL-8, the ATF3, I believe one of 20 the CXCL2s or 3. So some of them 21 were common. Other ones were not. 22 BY MR. SMITH: 23 Q. Okay. You provided an 24 affidavit to me in the Brower case, and</p>	<p>1 of the Shukla paper. Do you recall that? 2 A. Yeah. 3 Q. There were like a bunch of 4 them. 5 A. It was -- it was the same 6 paper xeroxed many times. Yes. 7 Q. And so this was just earlier 8 drafts or the drafts that eventually 9 became the Shukla paper that we just went 10 over, correct? 11 A. Yes. 12 (Document marked for 13 identification as Exhibit 14 Mossman-42.) 15 BY MR. SMITH: 16 Q. Okay. I'm going to attach 17 this as Exhibit 42. And it's entitled, 18 "Alterations in Gene Expression in Human 19 Mesothelial Cells Correlate With Mineral 20 Pathogenicity." 21 It has Shukla at the 22 beginning and looks almost exactly like 23 the study that we attached as Exhibit 34, 24 that was a peer-reviewed published</p>

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<p>1 publication, correct?</p> <p>2 A. Yes.</p> <p>3 Q. Okay. And if you go to</p> <p>4 Page 3, and look at the first large</p> <p>5 paragraph in the last sentence.</p> <p>6 A. Mm-hmm.</p> <p>7 Q. "Moreover, the early</p> <p>8 molecular events leading to injury by</p> <p>9 asbestos fibers and other pathogenic or</p> <p>10 innocuous particulates in human cells</p> <p>11 that may be targets for the development</p> <p>12 of disease remain enigmatic."</p> <p>13 And that's the reason you</p> <p>14 performed this study to look at those</p> <p>15 changes, right?</p> <p>16 A. We were interested in gene</p> <p>17 profiling, yes, that's correct.</p> <p>18 Q. Okay. And if you go to the</p> <p>19 second paragraph, and you go just past</p> <p>20 Number 6. It's one, two, three, four,</p> <p>21 five, six lines down.</p> <p>22 "This cell type is not</p> <p>23 implicated in asbestos-induced diseases,</p> <p>24 but is occasionally linked to the</p>	<p>1 MR. FROST: Objection.</p> <p>2 THE WITNESS: I believe it</p> <p>3 is in the Hillegass paper. And I</p> <p>4 seem to remember when I looked</p> <p>5 over this correspondence that this</p> <p>6 was a comment that one of the</p> <p>7 reviewers questioned, and he put</p> <p>8 in additional references.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. I thought we might go to the</p> <p>11 reviewer comments because we have it</p> <p>12 attached as Exhibit 36.</p> <p>13 A. Yeah. I remember that.</p> <p>14 Q. Show me in the reviewer</p> <p>15 comments where they say take that out.</p> <p>16 A. The Hillegass paper. They</p> <p>17 asked us --</p> <p>18 Q. No, ma'am. Ma'am.</p> <p>19 A. No.</p> <p>20 Q. This is Shukla.</p> <p>21 A. Yeah.</p> <p>22 Q. This is the Shukla paper.</p> <p>23 This is the draft of the Shukla paper.</p> <p>24 And that statement is in a draft of the</p>
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<p>1 inflammation and development of ovarian</p> <p>2 cancer after use of talcum powder in the</p> <p>3 pelvic region, albeit highly</p> <p>4 controversial."</p> <p>5 Why didn't that statement</p> <p>6 make it into the final?</p> <p>7 MR. FROST: Objection.</p> <p>8 THE WITNESS: This cell type</p> <p>9 is not implicated...</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Can you tell me why that</p> <p>12 statement, and I went through all of</p> <p>13 them, and that's the only statement,</p> <p>14 otherwise they read just exactly alike.</p> <p>15 "This cell type is not implicated in</p> <p>16 asbestos-induced diseases, but is</p> <p>17 occasionally linked to inflammation and</p> <p>18 the development of ovarian cancer after</p> <p>19 use of talcum powder in the pelvic</p> <p>20 region, albeit highly controversial."</p> <p>21 I want to know why that</p> <p>22 statement was taken out of the drafts and</p> <p>23 not in the final peer-reviewed</p> <p>24 publication.</p>	<p>1 Shukla paper that you provided me per the</p> <p>2 affidavit that we just went over in</p> <p>3 Exhibit 41.</p> <p>4 And I want you to show me in</p> <p>5 the Shukla paper that we just went over,</p> <p>6 it's peer reviewed, Exhibit Number 34 --</p> <p>7 A. Yeah.</p> <p>8 Q. -- where that statement is</p> <p>9 in that study that's in the draft that</p> <p>10 you provided to me.</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: Okay. So I'm</p> <p>13 looking at the Shukla paper, and</p> <p>14 that statement was Merritt in 2009</p> <p>15 and it is in this. So...</p> <p>16 BY MR. SMITH:</p> <p>17 Q. Where is it?</p> <p>18 A. All right. Let me just</p> <p>19 look. It's Reference Number 7?</p> <p>20 It says -- although I'm</p> <p>21 admitting that you looked this -- looked</p> <p>22 this over very well. It says, "This cell</p> <p>23 type is not implicated in</p> <p>24 asbestos-induced diseases but is</p>

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<p style="text-align: right;">Page 414</p> <p>1 occasionally linked to inflammation and</p> <p>2 the development of ovarian cancer after</p> <p>3 use of talcum powder in the pelvic</p> <p>4 region, although such links are highly</p> <p>5 controversial."</p> <p>6 Q. Where is it?</p> <p>7 A. It's in the final</p> <p>8 publication, exactly where I --</p> <p>9 Q. I know. Point me to it. I</p> <p>10 just missed it. Where is it?</p> <p>11 A. Yeah, I guess you did.</p> <p>12 Q. I guess I did. I'm -- I am</p> <p>13 mortal. I apologize.</p> <p>14 Where is it?</p> <p>15 A. Here you go.</p> <p>16 Q. Can you show me? Can you</p> <p>17 tell me where the --</p> <p>18 A. It's exactly where it was in</p> <p>19 the draft, yeah.</p> <p>20 MR. FROST: If you look at</p> <p>21 Page 1, right-hand column. It's</p> <p>22 the first full paragraph, last</p> <p>23 sentence.</p> <p>24 BY MR. SMITH:</p>	<p style="text-align: right;">Page 416</p> <p>1 MR. FROST: Take a short</p> <p>2 break.</p> <p>3 MR. SMITH: Sure. We can</p> <p>4 take a quick break.</p> <p>5 THE VIDEOGRAPHER: Going off</p> <p>6 the record. The time is 4:23.</p> <p>7 (Short break.)</p> <p>8 THE VIDEOGRAPHER: We are</p> <p>9 going back on record. Beginning</p> <p>10 of Media File Number 5. The time</p> <p>11 is 4:38.</p> <p>12 BY MR. SMITH:</p> <p>13 Q. Okay. So in Exhibit 39,</p> <p>14 which is a chart in your study, I need to</p> <p>15 correct --</p> <p>16 A. Yes.</p> <p>17 Q. I need to switch 24 to</p> <p>18 eight --</p> <p>19 A. Right.</p> <p>20 Q. -- and eight to 24, right?</p> <p>21 A. Yes. That's correct.</p> <p>22 Q. And I made those changes.</p> <p>23 Okay. And then over here,</p> <p>24 I've got a question in -- you have tale</p>
<p style="text-align: right;">Page 415</p> <p>1 Q. I missed it. I stand</p> <p>2 corrected.</p> <p>3 A. Wow.</p> <p>4 Q. I highlighted it right</p> <p>5 before it. Thank you.</p> <p>6 A. You're welcome.</p> <p>7 Q. Do you agree with that</p> <p>8 statement, now that it's -- we've</p> <p>9 established that it's in your study?</p> <p>10 A. I agree that it's highly</p> <p>11 controversial still.</p> <p>12 Q. Do you agree that it's been</p> <p>13 occasionally linked to inflammation in</p> <p>14 the development of ovarian cancer use</p> <p>15 after the use of talcum powder in the</p> <p>16 pelvic region?</p> <p>17 A. I believed in 2009, we</p> <p>18 referenced or we looked at the Ness and</p> <p>19 Cottreau, which was a hypothesis paper</p> <p>20 and it is still a hypothesis that the</p> <p>21 scientific data does not support.</p> <p>22 Q. Okay. Let's talk about --</p> <p>23 MR. SMITH: Are we okay? Or</p> <p>24 can we keep going?</p>	<p style="text-align: right;">Page 417</p> <p>1 at low concentrations of ovarian</p> <p>2 epithelial cells, zero.</p> <p>3 Do you see that?</p> <p>4 A. It should be -- it should be</p> <p>5 high because we only added talc to the</p> <p>6 ovarian epithelial cells at high</p> <p>7 concentrations. So these -- they're the</p> <p>8 right word, but they need to come down a</p> <p>9 little bit.</p> <p>10 Q. I'm with you.</p> <p>11 A. See.</p> <p>12 Q. So this should be -- right</p> <p>13 here this should be zero right here?</p> <p>14 A. Right.</p> <p>15 Q. And that should be -- that</p> <p>16 mark right there is for low</p> <p>17 concentration?</p> <p>18 A. Right. Right. Right.</p> <p>19 So in this case, yes.</p> <p>20 Q. All right. If you look at</p> <p>21 your paper --</p> <p>22 A. Yeah.</p> <p>23 Q. -- and you go to --</p> <p>24 A. Which one? The Shukla?</p>

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<p style="text-align: right;">Page 418</p> <p>1 Q. Shukla. 2 A. Okay. 3 MR. MIZGALA: I think it was 4 right the way it was. 5 THE WITNESS: High had no 6 results. 7 MR. SMITH: That's right. 8 BY MR. SMITH: 9 Q. All right. These are the 10 epithelial -- ovarian epithelial cells, 11 right? 12 A. Yes. 13 Q. Okay. And at 24 hours you 14 have zero at high concentrations, right? 15 Cell -- gene changes, right? 16 A. Yes. 17 Q. Okay. If you look at Page 5 18 of 10. 19 A. Yes. 20 Q. And it says, "At 21 24 hours" -- down at the bottom under 22 "IOSE ovarian epithelial cells exhibit 23 few gene expression changes," it says, 24 "At 24 hours, high concentrations of</p>	<p style="text-align: right;">Page 420</p> <p>1 A. This is the -- 2 MR. FROST: Objection. 3 THE WITNESS: -- gene -- 4 you're talking about the toxicity 5 data here. We did -- and I 6 believe it's stated in this paper. 7 We did a range of concentrations 8 with the talc up to 20. And I 9 think we make the statement that 10 in no cases was there toxicity to 11 the ovarian epithelial cells. So 12 it's here somewhere. 13 BY MR. SMITH: 14 Q. Well, my question is also, I 15 didn't think you tested talc at high 16 concentrations. 17 A. We only did that in the 18 ovarian epithelial cells, because of -- 19 we, in all of these, we had done 20 preliminary studies, and our original 21 ones indicated that we had no toxicity 22 and no effect. So we did the whole 23 experiment for microarrays at the high 24 concentration.</p>
<p style="text-align: right;">Page 419</p> <p>1 asbestos caused less than fourfold 2 increases in expression of only 16 genes 3 and decreased" -- hold on. Am I in the 4 right spot? No, I'm not. 5 Let's go back to 4 of 10. 6 I'm sorry. 7 A. Okay. 8 Q. "Asbestos fibers at high 9 concentrations are toxic to TP9/TERT-1 10 mesothelial cells and less so to ovarian 11 epithelial cells in contrast to particle 12 preparations." 13 It talks about, "Non-fibrous 14 talc at 75 micrometers squared per 15 centimeter squared was nontoxic, and 16 significant increases in toxicity were 17 only achieved with addition of talc at 18 greater than threefold concentrations in 19 LP9/TERT-1 cells (Figure 2A), but not in 20 IOSE cells (data not shown)." 21 A. Right. 22 Q. Okay. Is that -- data 23 not -- how -- where is this data to be 24 able to put zero down here? I don't --</p>	<p style="text-align: right;">Page 421</p> <p>1 Q. Where is that data that 2 shows that? 3 A. Okay. It's probably in here 4 somewhere. 5 Q. And data -- 6 A. Here we go. 7 Q. Data not shown or 8 referenced, where can I get that data? 9 A. I believe some of it might 10 have been in supplementary data in this 11 journal. 12 Q. Can you give me a 13 supplemental journal where that -- 14 A. Wait. Let me just make sure 15 then. Figure 2D. Okay. So, in terms of 16 the toxicity data for talc, it is in 17 Figure 2D, and that's the ovarian 18 epithelial cells. So there is data 19 presented on the cytotoxicity. 20 Q. Well, hold on a second, 21 because Table 6 it says -- in your -- 22 right here on Exhibit 39. Table 6, "Talc 23 does not cause altered gene expression in 24 human mesothelial or ovarian epithelial</p>

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<p style="text-align: right;">Page 422</p> <p>1 cells."</p> <p>2 We're not talking about</p> <p>3 toxicity. We're talking about gene</p> <p>4 expression changes.</p> <p>5 A. Right.</p> <p>6 Q. And you're writing zero down</p> <p>7 right here that you tested talc at high</p> <p>8 concentrations and got zero gene</p> <p>9 expression changes.</p> <p>10 My question is, where is</p> <p>11 that?</p> <p>12 A. Not in -- it says -- okay.</p> <p>13 (Reading to herself.)</p> <p>14 Okay. So if it didn't have</p> <p>15 any significant gene changes, like for</p> <p>16 the other materials, it wouldn't have</p> <p>17 been presented, because there was no</p> <p>18 significant increase in any of the genes.</p> <p>19 Q. Well, you have zero here.</p> <p>20 Where is that? Where does it show that</p> <p>21 there are no -- no changes? Where does</p> <p>22 it state that?</p> <p>23 A. It's stated here. Hold on.</p> <p>24 I think we've got it with the asbestos.</p>	<p style="text-align: right;">Page 424</p> <p>1 were just discussing, and it says data</p> <p>2 not shown.</p> <p>3 A. Right. No significant gene</p> <p>4 upregulation or downregulation in</p> <p>5 response to lower concentrations of</p> <p>6 asbestos. So no significant changes,</p> <p>7 data not shown. At high concentrations</p> <p>8 are what is expressed in Table 4.</p> <p>9 Q. Where are you reading that?</p> <p>10 A. I'm reading this on 5 of 10</p> <p>11 under IOSE ovarian epithelial cells.</p> <p>12 Q. It says, "Data not shown,"</p> <p>13 correct?</p> <p>14 A. That's correct.</p> <p>15 Q. Where can I get that data?</p> <p>16 A. It could be supplemental or</p> <p>17 it may not have been presented at all.</p> <p>18 Q. Would I have -- would there</p> <p>19 be any notes or lab notes or anything, or</p> <p>20 where -- I mean, I haven't seen an</p> <p>21 updated study of where that -- where you</p> <p>22 get zero here, besides a statement. I</p> <p>23 don't see like any testing or tables.</p> <p>24 MR. FROST: Objection.</p>
<p style="text-align: right;">Page 423</p> <p>1 Okay. Let me just see if it's in the --</p> <p>2 Okay. So, yeah. So this is important to</p> <p>3 look at, because in Table 4 at the high</p> <p>4 concentrations, you see only one number</p> <p>5 at the top, and the 2s are not</p> <p>6 significantly elevated.</p> <p>7 So the data is just shown at</p> <p>8 the high concentrations of materials. At</p> <p>9 the low concentrations there were no gene</p> <p>10 changes.</p> <p>11 Q. I understand that. But</p> <p>12 where -- I see the genes upregulated by</p> <p>13 crocidolite asbestos and IOSE human</p> <p>14 ovarian cells.</p> <p>15 A. Yes.</p> <p>16 Q. I do not a -- I do not see a</p> <p>17 table or a sentence about zero being</p> <p>18 found for talc.</p> <p>19 A. It's stated.</p> <p>20 Q. Where?</p> <p>21 A. In the results. Let's look</p> <p>22 where we describe the IO cells.</p> <p>23 All right.</p> <p>24 Q. I thought that's what we</p>	<p style="text-align: right;">Page 425</p> <p>1 THE WITNESS: I think it's</p> <p>2 the same thing that I explained to</p> <p>3 you before, is that we got no</p> <p>4 significant gene changes looking</p> <p>5 at thousands of genes, and that</p> <p>6 you don't -- you present in these</p> <p>7 findings what you did find, which</p> <p>8 are what you see in all these</p> <p>9 figures.</p> <p>10 So for any gene expression</p> <p>11 data, you're not going to see</p> <p>12 numbers or negative numbers for</p> <p>13 5,000 or some odd genes. It's --</p> <p>14 you don't express it like that.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. So there was data. It just</p> <p>17 wasn't included in this study.</p> <p>18 A. No. It was included in the</p> <p>19 statistical analyses, but it was</p> <p>20 insignificant; therefore, it was not</p> <p>21 graphed, because the numbers were at the</p> <p>22 ordinate of each graph.</p> <p>23 Q. I want to talk about the</p> <p>24 Hillegass study.</p>

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<p>1 A. Okay.</p> <p>2 MS. O'DELL: Excuse me for a</p> <p>3 moment. We Request that data that</p> <p>4 Dr. Mossman has just testified to,</p> <p>5 including the raw data, any</p> <p>6 statistical analyses and outputs</p> <p>7 of where the affected data has</p> <p>8 been noted.</p> <p>9 THE WITNESS: This paper was</p> <p>10 15 years ago. So there's not</p> <p>11 going to be any data. We did the</p> <p>12 literature search to try and find</p> <p>13 it.</p> <p>14 MS. O'DELL: The -- there's</p> <p>15 data that's published in the table</p> <p>16 in her report that's not reflected</p> <p>17 in the peer-reviewed publication,</p> <p>18 and we want to know what the</p> <p>19 underlying basis is for that data.</p> <p>20 So that's the question.</p> <p>21 MR. FROST: We'll take it</p> <p>22 under advisement. Just send a</p> <p>23 letter, take it under advisement.</p> <p>24 Or an e-mail.</p>	<p>1 was pathogenic, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And since talc was not</p> <p>4 subject to this test, we don't know what</p> <p>5 cytokines would have been released with</p> <p>6 exposure to talc and its relevance to</p> <p>7 talc's ability to cause disease from this</p> <p>8 study, correct?</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: Right. The</p> <p>11 levels of gene expression by talc</p> <p>12 were so small that we would not</p> <p>13 have expected an increase in terms</p> <p>14 of proteins.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. That -- that wasn't my</p> <p>17 question.</p> <p>18 My question was, since</p> <p>19 talc --</p> <p>20 MR. SMITH: And I object to</p> <p>21 nonresponsiveness.</p> <p>22 BY MR. SMITH:</p> <p>23 Q. Since talc was not subjected</p> <p>24 to this test, we do not know what</p>
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<p>1 BY MR. SMITH:</p> <p>2 Q. Let's move to the Hillegass</p> <p>3 study. And that's Exhibit 35. What type</p> <p>4 of asbestos did you look at in this</p> <p>5 study?</p> <p>6 A. It's crocidolite.</p> <p>7 Q. And is crocidolite one of</p> <p>8 the asbestos types that is found in Baby</p> <p>9 Powder or Shower to Shower that we</p> <p>10 discussed earlier?</p> <p>11 A. Not to my knowledge.</p> <p>12 Q. And you told me earlier that</p> <p>13 different types of asbestos affect human</p> <p>14 cells in different ways, correct?</p> <p>15 A. Yes. Our studies have been</p> <p>16 with chrysotile and crocidolite asbestos,</p> <p>17 and amosite, which falls into the same</p> <p>18 category as crocidolite in terms of</p> <p>19 results on cells.</p> <p>20 Q. Hillegass study involved</p> <p>21 gene profiling and proteomics, bioplex</p> <p>22 proteins, cytokines released from</p> <p>23 peritoneal mesothelial cells exposed to</p> <p>24 asbestos to determine if asbestos was --</p>	<p>1 cytokines would have been released with</p> <p>2 exposure to talc and its relevance to</p> <p>3 talc's ability to cause disease from this</p> <p>4 study, correct?</p> <p>5 MR. FROST: Objection.</p> <p>6 THE WITNESS: Again, we</p> <p>7 didn't look at that because the</p> <p>8 results were reversible and not of</p> <p>9 a magnitude that one would expect</p> <p>10 protein to be increased.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Okay. I asked you this</p> <p>13 question in Brower, do you recall that?</p> <p>14 MR. FROST: Objection.</p> <p>15 THE WITNESS: No.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. Okay. Look at Page 195 of</p> <p>18 your testimony in Brower. 194 and 195.</p> <p>19 A. Okay. 194 and 195?</p> <p>20 Q. Correct.</p> <p>21 A. Okay.</p> <p>22 Q. And I'm going to start on</p> <p>23 Line --</p> <p>24 A. Okay.</p>

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<p style="text-align: right;">Page 430</p> <p>1 Q. -- 10 -- or I'm going to 2 start on Line 8. 3 Can we go -- "Question: Can 4 we go back to the Hillegass study? 5 "Answer: Sure. 6 "Question: There were 7 additional tests done on asbestos that 8 were not done for talc in the study; is 9 that correct? 10 "Answer: As I remember it, 11 yes. 12 "Okay. What additional 13 tests were done on asbestos that were not 14 performed on talc? 15 "Answer: We used what was 16 called a bioplex assay to examine 17 additional -- what are called 18 cytokines -- that were released from the 19 LP9 cell line after exposure to 20 crocidolite. 21 "Question: So given the 22 fact that you didn't do the similar test 23 on talc or the peritoneal mesothelial 24 cells, you can't tell me what additional</p>	<p style="text-align: right;">Page 432</p> <p>1 from talc, correct? 2 MR. FROST: Objection. 3 THE WITNESS: I'm sorry. 4 I'm -- 5 MR. FROST: Do you want to 6 see the question or have it 7 read -- 8 THE WITNESS: Yeah. In your 9 studies, that being -- 10 BY MR. SMITH: 11 Q. In your studies you were 12 able to get additional information about 13 whether asbestos was carcinogenic to 14 cells, thought to be the origin of 15 ovarian cancer, that you failed to obtain 16 from talc, correct? 17 A. We weren't looking at 18 additional -- we weren't looking at 19 whether asbestos was carcinogenic to 20 cells in these studies. We were trying 21 to determine whether the gene profiling 22 changes that we saw in the Shukla studies 23 were reflected by increased release of 24 proteins from the cells.</p>
<p style="text-align: right;">Page 431</p> <p>1 cytokines would have been released in 2 that regard?" 3 And there was an objection. 4 "The witness: Yeah. I 5 can't" -- 6 "Answer: I can't tell you 7 the additional cytokines that were 8 released by talc because we didn't look 9 at that." 10 Is that your answer? Is 11 that correct? 12 MR. FROST: Objection. 13 THE WITNESS: Yes. If it 14 had been indicated that there were 15 elevations like asbestos, we would 16 have done the studies with talc, 17 but that was not the case. 18 BY MR. SMITH: 19 Q. In your study -- studies, 20 and that being Hillegass, you were able 21 to get additional information about 22 whether asbestos was carcinogenic to 23 cells, thought to be the origin of 24 ovarian cancer, that you failed to obtain</p>	<p style="text-align: right;">Page 433</p> <p>1 Q. Go to Page 196 of the Brower 2 testimony. 3 A. Mm-hmm. Okay. 196? 4 Q. Yes, ma'am. 5 A. Okay. 6 Q. Line 3. 7 A. Mm-hmm. 8 Q. "Question: So you were able 9 to get additional information about 10 whether or not crocidolite asbestos was 11 carcinogenic or not compared to 12 neomesothelial cells by doing these 13 additional studies? 14 "Answer: In general, yes." 15 Is that your answer? Is 16 that correct? 17 Is that statement correct 18 that you stated in Brower? 19 A. We were getting additional 20 information. Certainly from the study, 21 but the way your sentence is worded, your 22 question is worded, about whether or not 23 crocidolite asbestos was carcinogenic or 24 not, was not a focus of these studies</p>

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<p style="text-align: right;">Page 434</p> <p>1 whereby -- or would be gained by 2 information on these additional studies. 3 MR. SMITH: I'm going to 4 object as nonresponsive. 5 BY MR. SMITH: 6 Q. I'm going to read the 7 question and answer again. 8 "So you weren't able to get 9 additional information about whether or 10 not crocidolite asbestos was carcinogenic 11 or not compared to neomesothelial cells 12 by doing these additional studies?" And 13 we're talking about Hillegass. And your 14 answer was: "In general, yes." 15 Is that true, is that a true 16 statement? 17 MR. FROST: Objection. 18 THE WITNESS: Yeah. Let me 19 emphasize again that the 20 additional information we were 21 getting was whether genes that we 22 saw in Shukla resulted in protein 23 secretion by mesothelial cells 24 after exposure to crocidolite</p>	<p style="text-align: right;">Page 436</p> <p>1 Q. I think we attached it as an 2 exhibit to the deposition. 3 A. All right. Mm-hmm. If I 4 can find it in the pile here. Okay. 5 Q. When did you draft your 6 report and reach your conclusions? It's 7 dated February 25th, 2019. I think you 8 said some time in December or January 9 2018, 2019. Would that be correct? 10 A. Sometime in that realm, yes. 11 Q. What methodology did you use 12 in arriving at your opinions in this 13 case? 14 A. I used the same methodology 15 that I would have in our researching any 16 scientific review. 17 Q. And what is that? 18 A. Search of the peer-reviewed 19 literature on the topic. I was also 20 asked to comment on two expert reports. 21 And in that case, I looked at each 22 statement, each reference, and then I did 23 a literature review of my own to pull up 24 other possibly relevant papers.</p>
<p style="text-align: right;">Page 435</p> <p>1 asbestos. 2 This is a long leap in terms 3 of determining whether or not 4 crocidolite asbestos is 5 carcinogenic to peritoneal 6 mesothelial cells. We weren't 7 looking at that in these studies. 8 BY MR. SMITH: 9 Q. Can I rely on your answer in 10 the Brower case? 11 MR. FROST: Objection. 12 THE WITNESS: I'm qualifying 13 it. I say in general. 14 Again, I'm trying to make it 15 clear that we were looking at 16 proteins that were released from 17 these cells. Are there links 18 between these and cancer-causing 19 effects? Not necessarily. And 20 that's my answer. 21 BY MR. SMITH: 22 Q. All right. I would like to 23 talk to you about your report. 24 A. Okay.</p>	<p style="text-align: right;">Page 437</p> <p>1 So my methodology was the 2 same as I would have done in this case in 3 review of scientific papers submitted by 4 others to journals. 5 I'm missing my report here. 6 Q. Can you -- how did you 7 compile the literature or compile the 8 literature search that you did in this 9 area? 10 A. I did a PubMed search. 11 Q. Of what? 12 A. I looked at asbestos and 13 ovarian cancer. I put in talc and 14 ovarian cancer. I looked at all the 15 references that were cited by 16 Drs. Zelikoff and Saed and read those 17 papers, and then I looked at statements 18 in those papers and how they were 19 referenced. So I had an additional 20 volume of information. 21 Q. You said that you used the 22 methodology that you used in your 23 peer-reviewed literature; is that 24 correct?</p>



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<p style="text-align: right;">Page 438</p> <p>1 A. I used the peer-review 2 process in order to compile the work. I 3 cited work that I'd done in peer-reviewed 4 journals. And I also -- thank you. 5 And I also looked at the 6 IARC -- two reports, which are not peer 7 reviewed. 8 Q. The IARC monograph is not 9 peer-reviewed? 10 A. No, it's not. It's not in a 11 peer-reviewed database. 12 Q. Are your opinions in this 13 case peer reviewed? Is your report peer 14 reviewed? 15 A. My report is based upon my 16 review of peer-reviewed data. 17 Q. Is your report in this case 18 a peer-reviewed study? 19 A. It's not. It's an opinion, 20 or set of opinions. 21 Q. In your opinion -- and we'll 22 look at it in a minute. I don't see 23 anywhere in your -- and I could be wrong, 24 like I missed something before earlier,</p>	<p style="text-align: right;">Page 440</p> <p>1 Q. Do the Shukla and Hillegass 2 studies play a major role in the basis of 3 your opinions in this case? 4 MR. FROST: Objection. 5 THE WITNESS: They add basis 6 to the studies that I reviewed. 7 So I would include these as well 8 as the animal studies and the 9 epidemiology and other mechanistic 10 studies as related to my final 11 opinions. 12 BY MR. SMITH: 13 Q. Did you examine all the 14 available data on cells responsible for 15 ovarian cancer and its interaction with 16 cosmetic-grade talc, that being the type 17 that's in Baby Powder and Shower to 18 Shower? 19 A. Could you state that again. 20 I'm sorry. 21 Q. Did you explain all the 22 available data on cells responsible for 23 ovarian cancer and its interaction with 24 cosmetic-grade talc, that being the type</p>
<p style="text-align: right;">Page 439</p> <p>1 but I didn't see anywhere in your report 2 where you state that you do not believe 3 that talc -- there's no statement that I 4 recall that you do not hold the opinion 5 that talc does not cause ovarian cancer. 6 MR. FROST: Objection. 7 BY MR. SMITH: 8 Q. Do you recall that being 9 stated in your report? 10 A. I don't. But I'd have to go 11 through it. 12 Q. Are all your opinions in 13 this case contained in that report? 14 A. Yes. I'm wondering whether 15 it's in the summary or the end of the 16 reports. 17 Q. We'll go through your bullet 18 points -- 19 A. Okay. 20 Q. -- and we'll come back to 21 that. 22 A. Okay. It might be in there. 23 I just don't know where it would be 24 stated in terms of that precise sentence.</p>	<p style="text-align: right;">Page 441</p> <p>1 that's in Baby Powder and Shower to 2 Shower? 3 A. If I pulled the information 4 up on PubMed, if there was research out 5 there, I would have pulled it up. I 6 don't recall any studies in vitro that 7 focused on cosmetic talc with the 8 exception of Dr. Saed's. 9 Q. Did you examine all the 10 available data on cells responsible for 11 ovarian cancer and its interaction of the 12 types of asbestos found in Baby Powder 13 and Shower to Shower? 14 A. That's not a simple yes or 15 no question. Again, if there were papers 16 that were in the peer-reviewed scientific 17 literature on talcs, I would have gotten 18 those. Whether they were specifically 19 regarding cosmetic talcs or industrial 20 talcs or pharmaceutical-grade talcs, that 21 would have been in the papers themselves. 22 Q. Let's go to your report. 23 A. Okay. 24 Q. I'd like to go to Bullet</p>

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<p style="text-align: right;">Page 442</p> <p>1 Point 1, summary of opinions. Bullet</p> <p>2 Point 1: "Cosmetic talc particles and</p> <p>3 non-asbestos cleavage fragments are</p> <p>4 different chemically, physically, and</p> <p>5 structurally from amphibole asbestos</p> <p>6 types, crocidolite and amosite."</p> <p>7 You mentioned cosmetic talc</p> <p>8 particles, but you have never studied</p> <p>9 cosmetic talc particles; is that correct?</p> <p>10 MR. FROST: Objection.</p> <p>11 THE WITNESS: Correct. But</p> <p>12 they are -- I again reviewed the</p> <p>13 IARC report and reports by</p> <p>14 Zazenski, et al., characterizing</p> <p>15 cosmetic talcs, and they are --</p> <p>16 that's where this statement came</p> <p>17 from.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. And you mentioned</p> <p>20 crocidolite and amosite asbestos,</p> <p>21 correct?</p> <p>22 A. Yes.</p> <p>23 Q. And we mentioned earlier</p> <p>24 this is not the type of asbestos that's</p>	<p style="text-align: right;">Page 444</p> <p>1 reactions.</p> <p>2 Q. And analyzing whether a</p> <p>3 sample of materials is talc, asbestos, or</p> <p>4 talc with asbestos, you leave that to</p> <p>5 mineralogists, as we discussed that</p> <p>6 earlier, correct?</p> <p>7 A. Yes. I work with reference</p> <p>8 samples of materials.</p> <p>9 Q. And the same for determining</p> <p>10 if a mineral is asbestos or asbestiform,</p> <p>11 correct?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: Yes. The</p> <p>14 mineralogists I collaborate with</p> <p>15 characterize these materials.</p> <p>16 BY MR. SMITH:</p> <p>17 Q. And you're not a geologist?</p> <p>18 A. That's correct.</p> <p>19 Q. And not a materials analyst,</p> <p>20 correct?</p> <p>21 A. Correct.</p> <p>22 Q. And you are not an expert in</p> <p>23 determining the flexibility or rigidity</p> <p>24 of asbestos or cleavage fragments,</p>
<p style="text-align: right;">Page 443</p> <p>1 been found in Baby Powder and Shower to</p> <p>2 Shower; is that correct?</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: Again, you're</p> <p>5 assuming that other asbestos types</p> <p>6 have been found in these</p> <p>7 materials, and I am unaware of</p> <p>8 that data.</p> <p>9 BY MR. SMITH:</p> <p>10 Q. Okay. Bullet Point 1, you</p> <p>11 mention the different chemical, physical,</p> <p>12 and structural differences of cosmetic</p> <p>13 talc and crocidolite asbestos and amosite</p> <p>14 asbestos, correct?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Yes.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. And you stated you are not a</p> <p>19 mineralogist, correct?</p> <p>20 A. No, but I have interacted</p> <p>21 with mesothelial cell, let's say,</p> <p>22 biologists and geologists who have</p> <p>23 emphasized in their experiments or</p> <p>24 characterization that they're different</p>	<p style="text-align: right;">Page 445</p> <p>1 correct?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: I have not</p> <p>4 used methods in my lab -- measure</p> <p>5 particle flexibility directly.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Let's go to Bullet Point 2.</p> <p>8 "Because of these different properties,</p> <p>9 cosmetic talc particles and non-asbestos</p> <p>10 cleavage fragments are unlikely to reach</p> <p>11 or be retained at sites of development of</p> <p>12 mesothelioma or ovarian cancers."</p> <p>13 You stated that you never</p> <p>14 studied cosmetic talc particles or</p> <p>15 cleavage fragments that have been</p> <p>16 reported in Baby Powder or Shower to</p> <p>17 Shower, correct?</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: I myself</p> <p>20 haven't studied them. But others</p> <p>21 have, and their properties have</p> <p>22 been documented by others,</p> <p>23 including mineralogists.</p> <p>24 BY MR. SMITH:</p>

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<p style="text-align: right;">Page 446</p> <p>1 Q. What is the basis of that</p> <p>2 statement?</p> <p>3 A. The basis of the statement</p> <p>4 is twofold. Cosmetic talc particles as</p> <p>5 defined in IARC are platelike, large</p> <p>6 platelike discs that would not be</p> <p>7 deposited as would amphibole asbestos</p> <p>8 types at the pleura. They would not make</p> <p>9 it out to the pleura because of their</p> <p>10 size. And this is true of non-asbestos</p> <p>11 cleavage fragments as well. Because</p> <p>12 experiments by Dr. Wiley have indicated</p> <p>13 that these cleavage fragments break</p> <p>14 perpendicular to the fiber surface. So</p> <p>15 they don't form long, thin fibers.</p> <p>16 And cleavage fragments of a</p> <p>17 size that are pathogenic; that is, 5 to</p> <p>18 10 microns are rare, if at all existent</p> <p>19 in diameters that would allow them to be</p> <p>20 taken out to the pleura by transfer or</p> <p>21 retained in the pleura.</p> <p>22 Q. You told me earlier in the</p> <p>23 depo that you had not studied how</p> <p>24 tremolite, anthophyllite, and actinolite</p>	<p style="text-align: right;">Page 448</p> <p>1 development of disease.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. And you also stated earlier</p> <p>4 that you had not performed any studies on</p> <p>5 whether cleavage fragments can reach the</p> <p>6 area of the lung where -- where</p> <p>7 mesothelioma is induced and developed.</p> <p>8 We discussed that earlier.</p> <p>9 MR. FROST: Objection.</p> <p>10 THE WITNESS: That's true,</p> <p>11 but other individuals have shown</p> <p>12 that cleavage fragments of a</p> <p>13 variety of types are not</p> <p>14 mesothelioma-genic.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. And what basis do you have</p> <p>17 to say that cosmetic-grade talc particles</p> <p>18 cannot be retained by the ovaries?</p> <p>19 MR. FROST: Objection.</p> <p>20 THE WITNESS: I am saying</p> <p>21 that there's no scientifically</p> <p>22 plausible pathway where they would</p> <p>23 be translocated in a retrograde</p> <p>24 fashion from the perineum to the</p>
<p style="text-align: right;">Page 447</p> <p>1 asbestos reached the areas of the lungs</p> <p>2 where mesothelioma is induced and</p> <p>3 developed, and you could not make a</p> <p>4 strict analogy to these type of asbestos</p> <p>5 from your study of other types of</p> <p>6 asbestos. We talked about that earlier</p> <p>7 in the deposition.</p> <p>8 MR. FROST: Objection.</p> <p>9 THE WITNESS: We did. But I</p> <p>10 want to emphasize that if these</p> <p>11 materials -- it's known that</p> <p>12 anthophyllite and tremolite are</p> <p>13 thicker, blunter fibers than the</p> <p>14 needlelike amphibole asbestos</p> <p>15 types and, therefore, their</p> <p>16 propensity to either reach or be</p> <p>17 retained at sites of development</p> <p>18 of mesothelioma would be related</p> <p>19 to their surface features, as well</p> <p>20 as their physical features and,</p> <p>21 therefore, them being blunt and</p> <p>22 thick, like cleavage fragments,</p> <p>23 they would be unlikely to reach or</p> <p>24 be retained at sites of</p>	<p style="text-align: right;">Page 449</p> <p>1 ovary.</p> <p>2 BY MR. SMITH:</p> <p>3 Q. Well, you state in your --</p> <p>4 in -- in the bullet point that fragments</p> <p>5 are unlikely to be reached -- reach or be</p> <p>6 retained by these sites of development of</p> <p>7 mesotheliomas or ovarian cancers. And</p> <p>8 I'm going to the or part. Or retained.</p> <p>9 What basis do you have to</p> <p>10 say that cosmetic-grade talc particles</p> <p>11 cannot be retained by the ovaries?</p> <p>12 MR. FROST: Objection.</p> <p>13 THE WITNESS: What I'm</p> <p>14 saying is that there has been no</p> <p>15 information suggesting that they</p> <p>16 get there to cause disease.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Have you not seen</p> <p>19 pathological studies of -- and we've gone</p> <p>20 through a bunch of them, where they have</p> <p>21 found talc in human ovarian tissue?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: Yes, and I'd</p> <p>24 like to emphasize that the IARC</p>

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<p style="text-align: right;">Page 450</p> <p>1 committee found that talc degrades 2 in a period of about eight years. 3 So my point here is that 4 we're talking about mesothelioma 5 in this case, in my second bullet. 6 And that they would not be 7 retained for periods of time 8 sufficient enough for the 9 development of mesothelioma. We 10 don't know what the latency period 11 is of ovarian cancer. 12 But the same thing is true, 13 that the amphibole asbestos types 14 that I've studied, crocidolite and 15 amosite, are durable in lung for 16 periods of time of decades, as 17 opposed to years with something 18 such as talc. 19 BY MR. SMITH: 20 Q. You understand about talc 21 exposure, we're talking about chronic 22 talc exposure over decades. Do you 23 understand that that's what we are 24 talking about?</p>	<p style="text-align: right;">Page 452</p> <p>1 particles in general showing that 2 their half life in the human body 3 is an approximately eight-year 4 time span for a platelike talc. 5 BY MR. SMITH: 6 Q. But that's talking about 7 dissolution, not about retention. 8 A. But retention and 9 dissolution are the same thing. If 10 something dissolves, it can't be 11 retained. It's one of the factors that's 12 very important. 13 Q. Do you know if any of those 14 studies on bio durability have discussed 15 or looked at talc in ovarian tissue to 16 determine how long it survives in ovarian 17 tissue? 18 A. No. Because the studies 19 that have shown it in ovarian tissues are 20 for probably decades since these 21 exposures. We have no idea. And the way 22 to address that question wouldn't be in 23 looking at human ovarian material. 24 Q. You have not performed any</p>
<p style="text-align: right;">Page 451</p> <p>1 A. You may be talking about it, 2 but I don't think there's evidence again 3 showing that chronic talc exposure leads 4 to migration to the ovary or that it's 5 associated with -- with disease. 6 Q. I'm just questioning your 7 opinion about fragments are unlikely, 8 non-asbestos cleavage fragments and 9 cosmetic talc particles, to be retained 10 at the sites of development of ovarian 11 cancer. 12 And I want to know what your 13 basis of opinion that cosmetic-grade talc 14 which you've never tested cannot be 15 retained by the ovaries. 16 MR. FROST: Objection. 17 BY MR. SMITH: 18 Q. When we have studies that 19 show talc in human ovarian tissue and -- 20 and human cancer tissue. 21 MR. FROST: Objection. 22 THE WITNESS: So what I'm 23 telling -- what I'm telling you is 24 that there are studies on talc</p>	<p style="text-align: right;">Page 453</p> <p>1 studies on whether or not asbestos 2 cleavage fragments can cause ovarian 3 cancer, correct? 4 MR. FROST: Objection. 5 THE WITNESS: I have not. 6 BY MR. SMITH: 7 Q. Third bullet point. "Talc 8 and non-asbestos cleavage fragments are 9 not reactive with cells and their 10 effective repair pathways occur. Because 11 they are distinct in chemistry and other 12 features from asbestos fibers, they do 13 not have the same potential to cause the 14 abnormal cell responses that are integral 15 to the development of cancers." 16 MR. FROST: Objection. 17 BY MR. SMITH: 18 Q. Is that your third bullet 19 point in your summary of opinions? 20 A. Yes. 21 Q. Okay. Well, talc not being 22 reactive with cells, we showed in Shukla 23 that talc was reactive with cells by 24 altering 30 genes at high concentrations</p>

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<p>1 at eight hours, right?</p> <p>2 A. And what I'm saying is that</p> <p>3 any particle would have caused those</p> <p>4 changes. That was inert. And the 30</p> <p>5 changes that we observed as opposed to</p> <p>6 hundreds of genes with asbestos was not</p> <p>7 significantly different than the</p> <p>8 responses of these cells to titanium</p> <p>9 dioxide or glass.</p> <p>10 Q. And we went over, titanium</p> <p>11 dioxide and glass did not alter any</p> <p>12 genes, correct?</p> <p>13 A. It did not alter any genes</p> <p>14 significantly. That's correct.</p> <p>15 Q. In regards to cleavage</p> <p>16 fragments, you stated you -- stated</p> <p>17 earlier you never studied anthophyllite</p> <p>18 or actinolite cleavage fragments, or</p> <p>19 tremolite --</p> <p>20 MR. FROST: Objection.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. -- besides the one study in</p> <p>23 New York?</p> <p>24 A. I have studied survival and</p>	<p>1 theme is primarily the national</p> <p>2 institutes that conducts research.</p> <p>3 And this was a road plan for</p> <p>4 research.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Well, they talk about the</p> <p>7 NIOSH REL, correct, and exposure to EMPs</p> <p>8 that meet the definition of fibrous talc</p> <p>9 in this -- in this document; is that</p> <p>10 correct?</p> <p>11 MR. FROST: Objection.</p> <p>12 THE WITNESS: I -- you would</p> <p>13 have to show me where that's</p> <p>14 specifically. I don't remember</p> <p>15 fibrous talc being used as a term</p> <p>16 in this document.</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Look on Page 33. Look at</p> <p>19 2.7.2, clarification of the current NIOSH</p> <p>20 REL. And it says at the top right</p> <p>21 column, "However, as the following</p> <p>22 clarified REL makes clear, particles that</p> <p>23 meet the specified dimensional criteria</p> <p>24 remain countable under the REL for the</p>
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<p>1 toxicity of three samples of New York</p> <p>2 State talc containing non-asbestiform</p> <p>3 tremolite and non-asbestos anthophyllite.</p> <p>4 Q. And that was studying</p> <p>5 industrial-grade talc, correct?</p> <p>6 A. That is correct.</p> <p>7 Q. And we discussed what NIOSH</p> <p>8 was earlier. Do you recall? I think we</p> <p>9 went through what NIOSH was. It was</p> <p>10 under OSHA. Do you recall that</p> <p>11 testimony?</p> <p>12 A. NIOSH stands for the</p> <p>13 National Institute of Occupational Safety</p> <p>14 and Health, yes.</p> <p>15 MR. FROST: Talking about</p> <p>16 the roadmap?</p> <p>17 THE WITNESS: I got it here.</p> <p>18 BY MR. SMITH:</p> <p>19 Q. NIOSH regulates exposures to</p> <p>20 EMPs that meet the definition which may</p> <p>21 include fibrous talc; is that correct?</p> <p>22 MR. FROST: Objection.</p> <p>23 THE WITNESS: OSHA is the</p> <p>24 regulatory agency. NIOSH, in my</p>	<p>1 reasons stated above, even if they're</p> <p>2 derived from non-asbestiform analogs of</p> <p>3 the asbestiform minerals. With the use</p> <p>4 of terms defined in this roadmap, the</p> <p>5 NIOSH REL is now clarified as follows."</p> <p>6 And it talks about, "NIOSH</p> <p>7 has determined that exposure to asbestos</p> <p>8 fibers can cause cancer and asbestosis in</p> <p>9 humans and recommends exposure be reduced</p> <p>10 to the lowest feasible concentration.</p> <p>11 NIOSH has designated asbestos to be a</p> <p>12 potential carcinogen and recommends that</p> <p>13 exposures be reduced to the lowest</p> <p>14 feasible concentration.</p> <p>15 "NIOSH REL for airborne</p> <p>16 asbestos fibers and elongated mineral</p> <p>17 particles is .1 countable EMP from one or</p> <p>18 more covered minerals per cubic</p> <p>19 centimeter averaged over 100 minutes."</p> <p>20 And it talks about a</p> <p>21 countable elongated mineral particle,</p> <p>22 EMP. And then it goes on to the next</p> <p>23 page, next bullet point.</p> <p>24 "A covered mineral is any</p>

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<p>1 mineral having the crystal structure and 2 elemental composition of one of the 3 asbestos varieties (chrysotile), 4 riebeckite asbestos (crocidolite)", I 5 can't pronounce all of these. All the 6 different asbestos -- "or one of their 7 non-asbestiform analogs and the amphibole 8 minerals contained in the mineral series, 9 the tremolite mineral series" -- and I 10 can't pronounce those names. 11 Is that correct? 12 MR. FROST: Objection. 13 THE WITNESS: I'm not sure 14 what this is saying. It says 15 clarification -- it's under a 16 section, "Clarification of the 17 current exposure limit." They do 18 state on Page 32 that they suggest 19 that -- "Studies suggest that 20 non-asbestiform amphiboles might 21 post different risks than 22 asbestos," and that was a theme 23 throughout this document. 24 BY MR. SMITH:</p>	<p>1 Sciences. And that questioned 2 statements such as this and 3 clarified them in the response of 4 that committee. 5 So there -- I would disagree 6 that NIOSH -- and in fact, I have 7 been convinced through the decades 8 that OSHA and NIOSH don't regulate 9 non-asbestiform analogs. 10 BY MR. SMITH: 11 Q. So you're telling me, in 12 your opinion, you do not believe that 13 non-asbestos cleavage fragments are 14 subject to REL -- the count for REL 15 regarding the exposure limits to human 16 workers to non-asbestiform cleavage 17 fragments? You don't believe that that 18 exists today? 19 MR. FROST: Objection. 20 THE WITNESS: I'm sorry, the 21 question is, what exists? 22 BY MR. SMITH: 23 Q. A time-weighted limit called 24 an REL on exposures of U.S. workers to</p>
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<p>1 Q. Absolutely. But they also 2 regulate -- do you understand that NIOSH 3 and REL is a time-weighted average 4 exposure to a worker by a mineral? Do 5 you understand that? 6 MR. FROST: Objection. 7 THE WITNESS: I understand 8 it, but I -- 9 BY MR. SMITH: 10 Q. But my question. 11 A. -- do not -- 12 Q. Hold on. My question -- you 13 understand that. 14 My question is, do you 15 understand that non-asbestiform cleavage 16 fragments are regulated under the NIOSH 17 REL for exposures to human workers? 18 MR. FROST: Objection. 19 THE WITNESS: No. I don't 20 think that's correct. As a matter 21 of fact after this report, there 22 was another report to address the 23 roadmap's strengths and weaknesses 24 by the National Academy of</p>	<p>1 these cleavage fragments -- 2 MR. FROST: Objection. 3 BY MR. SMITH: 4 Q. -- by NIOSH? 5 A. I don't know what those are. 6 And they're not stated here. So I can't 7 give you a NIOSH REL for non-asbestos 8 cleavage fragments. 9 Q. You can't tell me whether 10 the NIOSH -- whether you count a worker's 11 exposure to non-asbestos cleavage 12 fragments -- goes to the overall exposure 13 of a worker for the NIOSH REL or not? 14 MR. FROST: Objection. 15 THE WITNESS: That is not my 16 area of expertise. No, I can't 17 tell you that. And I can just 18 tell you that biologically, as is 19 stated in this report, it's stated 20 that these cleavage fragments 21 might pose different risks or 22 lesser risks than their asbestos 23 counterparts. 24 BY MR. SMITH:</p>

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<p>1 Q. It doesn't say no risk. In 2 fact, they're regulated per the NIOSH 3 document that I just showed you. 4 MR. FROST: Objection. 5 THE WITNESS: I -- I would 6 have to see that, whether that 7 still exists. That was a subject 8 of controversy, not only in this 9 document, but in a subsequent 10 document that looked at the 11 deliberations of this committee. 12 BY MR. SMITH: 13 Q. The French government 14 doesn't agree with you on your assessment 15 of the health risk of cleavage fragments, 16 do they? 17 MR. FROST: Objection. 18 THE WITNESS: I think French 19 scientists agree with me. 20 BY MR. SMITH: 21 Q. You have been shown the 22 ANSES articles and the publication, have 23 you not, and the official opinion of the 24 French agency for food, environmental,</p>	<p>1 health issues by assessing health risk 2 and benefits, often through the prism of 3 the human and social sciences. 4 "Its monitoring, diligence, 5 and surveillance work provides input for 6 risk assessment. ANSES work fully 7 addresses all types of risk, chemical, 8 biological, physical, et cetera, to which 9 a person may be subjected intentionally 10 or otherwise at all ages and stages of 11 life, including through exposure at work, 12 while traveling, while engaging in 13 leisure activities or via their diet." 14 Do you see that? 15 A. And I state that I have 16 never heard of ANSES prior to this 17 litigation. 18 Q. Okay. And if you look at 19 the second page, it talks about the 20 collaborative, impartial expert 21 assessment that they do. And then I want 22 to -- 23 A. I've interacted with many 24 scientists, including the leading</p>
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<p>1 and occupational health and safety? 2 A. That is not their 3 national -- Inserm is their national 4 research on fibers and particles. I have 5 no idea what ANSES is. 6 Q. Let's look at page -- at 7 document -- Exhibit 43. 8 (Document marked for 9 identification as Exhibit 10 Mossman-43.) 11 BY MR. SMITH: 12 Q. "The French Agency For Food, 13 Environmental, and Occupational Health 14 and Safety," A-N-S-E-S, "was created on 15 July 1st, 2010. It is an administrative 16 public establishment accountable to the 17 French Ministries of Health, Agriculture, 18 Environment, Labor and Consumer Affairs. 19 ANSES undertakes monitoring, expert 20 assessment, research, and reference 21 activities in a broad range of topics 22 that encompass human health, animal 23 health and wellbeing, and plant health. 24 It offers a cross-cutting perspective on</p>	<p>1 scientist in France at Inserm and never 2 have heard of this society or whatever it 3 is, an agency, and would question whether 4 it's a research agency. 5 (Document marked for 6 identification as Exhibit 7 Mossman-44.) 8 BY MR. SMITH: 9 Q. This is Exhibit 44. It's 10 the Director General of ANSES opinion. 11 It's an opinion of the French agency for 12 food, environmental and occupational 13 health and safety, on health effects 14 identified of cleavage fragments from -- 15 of amphiboles from quarried minerals. 16 It says, "ANSES undertakes 17 independent and pluralistic scientific 18 expert assessments. ANSES ensures 19 environmental, occupational and food 20 safety as well as assessing the potential 21 health risks they may entail. It also 22 contributes to the protection of the 23 health and welfare of animals, the 24 protection of plant health and the</p>

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<p>1 evaluation of the nutritional 2 characteristics of food. It provides the 3 competent authorities with all necessary 4 information concerning these risks as 5 well as the requisite expertise and 6 scientific and technical support for 7 drafting legislative and statutory 8 provisions and implementing risk 9 management societies." And for -- it 10 cites the French Public Health Code. 11 The opinions are made 12 public. And it states, "On August 28, 13 2014, ANSES was requested by the 14 Directorate General for Labour, the 15 Directorate General for Risk 16 Protection" -- "Prevention and 17 Directorate General for Health to 18 undertake the following expert appraisal: 19 Health effects and identification of 20 cleavage fragments of amphiboles from 21 quarried minerals." 22 And it goes on, the second 23 page, it says, "Against this background 24 the request included the following</p>	<p>1 document before? 2 MR. FROST: Objection. 3 THE WITNESS: I have. 4 Am I allowed to comment on 5 it? 6 MR. FROST: My objection was 7 to reading it. 8 THE WITNESS: Okay. 9 BY MR. SMITH: 10 Q. And then if you go onto the 11 page -- let's see. Seven pages in. It 12 says, "To sum up, the CES concludes that: 13 "In the current state of 14 knowledge concerning their health 15 effects, cleavage fragments of 16 non-asbestos amphiboles, actinolite, 17 anthophyllite, tremolite, grunerite and 18 riebeckite were meet" -- "meeting the 19 WHO's dimensional criteria for fibers 20 should not be distinguished from their 21 asbestiform counterparts." 22 And do you see that written 23 there? 24 Do you agree with that</p>
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<p>1 points: 2 "To review toxicological and 3 epidemiological evidence relating to 4 cleavage fragments of minerals with 5 non-asbestiform profiles: Actinolite, 6 anthophyllite, tremolite, grunerite, 7 riebeckite. What conclusions can be 8 reached about their effects on health? 9 "2, what current data are 10 available regarding the specific 11 exposures to cleavage fragments and 12 minerals cited above? 13 "3, are there routine 14 analytics methods that can be implemented 15 by laboratories accredited, capable of 16 distinguishing the fibers?" And -- and 17 they list the fibers there. 18 And it says, "On the 19 conclusion of the expert appraisal, 20 recommendations may be proposed 21 concerning the protection and prevention 22 of risks to health of persons exposed to 23 these cleavage fragments." 24 Have you ever seen this</p>	<p>1 assessment by them? 2 A. Can you point to the -- 3 MR. FROST: Objection. 4 THE WITNESS: -- statement 5 on Page 7 that you're talking 6 about? 7 There is no reason to make a 8 distinction? Is that what you're 9 talking about? 10 BY MR. SMITH: 11 Q. That statement right here. 12 It's, to sum up, the CES concludes that. 13 A. First of all, I don't know 14 what the CES is. This report was signed 15 by one individual. I have never heard of 16 this review or this assignment through a 17 scientific body. 18 And I also want to emphasize 19 that the references that are cited, if 20 you look at Page 12 and 13, their total 21 for this entire document of 14 or so 22 references, of which many are original 23 ANSES studies which appear to be related 24 to outcrops of asbestos.</p>

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<p style="text-align: right;">Page 470</p> <p>1 But more importantly, the 2 references they cite, by Addison and 3 McConnell, by Cyphert, by Davis, by 4 Ilgren, Kodavanti, by me, who my name is 5 spelled wrong. But we know that all of 6 these, and Williams, all say that 7 cleavage fragments do not pose a cancer 8 risk. 9 So this study, or whatever 10 it was, the conclusions of this 11 individual, are not based upon the 12 peer-reviewed scientific literature that 13 is cited. 14 Q. So you disagree with their 15 opinions about cleavage fragments? 16 A. I do. It's not supported by 17 their own references. 18 Q. Okay. I want to show you an 19 e-mail which I'm attaching as Exhibit 45. 20 (Document marked for 21 identification as Exhibit 22 Mossman-45.) 23 BY MR. SMITH: 24 Q. Series of e-mails. I want</p>	<p style="text-align: right;">Page 472</p> <p>1 cleavage fragments ought not to be 2 treated as asbestos.' Confusion and 3 misinformation persists. John Kelse" -- 4 who you know, correct? 5 A. I -- I knew him in the early 6 1990s. 7 Q. -- "sets out the facts for 8 non-asbestiform amphiboles, reviews 9 recent cases and warns against unreasoned 10 decisionmaking." 11 And he worked for who, who 12 did John Kelse work for? 13 A. When I corresponded with 14 him, I believe he worked for 15 R.T. Vanderbilt, but I'm not certain 16 whether that was his lifetime employer or 17 not. I have no idea. 18 Q. Says, "I can see how it 19 would be helpful, part of the ongoing 20 self-education process for ourselves and 21 our business partners to have something 22 like this as a reference. But I defer to 23 the experts like yourselves and advise if 24 you feel the article is accurate, helpful</p>
<p style="text-align: right;">Page 471</p> <p>1 you to go to the second page. It's by 2 Rich Zazenski. 3 Well, I want you to read the 4 whole thing. Let's start at the -- it's 5 going -- 6 A. Okay. 7 Q. You are going to go to the 8 back forward. 9 A. Okay. 10 MR. FROST: Objection. 11 BY MR. SMITH: 12 Q. And it's Peter Argust, 13 director of regulatory affairs from Rio 14 Tinto Minerals. 15 And it states -- from Peter 16 Argust to Rich Zazenski and Julie Pier 17 and some others, regarding the article of 18 industrial minerals asbestos. 19 Julie -- "Rich, Julie, and 20 Greg, our colleagues, Miguel Galindo has 21 shared with me the attached article in 22 Industrial Minerals magazine's 23 February 2008 edition. The subtitle, '15 24 years after OSHA ruled that common</p>	<p style="text-align: right;">Page 473</p> <p>1 or not. Could you give me your 2 professional reactions. Thanks and kind 3 regards, Peter, Peter Argust." 4 The response is from 5 Rich Zazenski at -- regulatory affairs 6 manager at Rio Tinto Minerals. And he's 7 got richzazenski@Luzenac.com as his 8 e-mail address. 9 He says, "I had seen and 10 read this article, and my first reaction 11 was 'who really wrote this paper for 12 John's signature?' I know John. He is a 13 fairly technical person, but excuse me, 14 he would not write such an article and 15 cite 129 references. The answer is 16 obvious, regardless I cannot agree with 17 his position. We just don't have enough 18 facts. Geologically it doesn't make 19 sense to me that you can have a mineral 20 deposit that just contains 21 non-asbestiform tremolite. 22 "I believe the USGS study of 23 talc from Death Valley, California, 24 nailed it correctly. That if a deposit</p>

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<p>1 contains 'non-asbestiform' tremolite, 2 there is also asbestiform tremolite 3 naturally present as well. And since 4 tremolite was never really a large 5 commercial mineral such as chrysotile or 6 crocidolite, there is not enough medical 7 data to conclude that 'blocky' tremolite 8 is simply a nuisance dust. 9 "But that has been the story 10 line for Vanderbilt for years and they 11 are sticking to it. I closely followed 12 the OSHA/Vanderbilt debate during the 13 1990s. Essentially OSHA 'threw in the 14 towel,' rather than expend their limited 15 resources on this issue. Their decision 16 by no means should be interpreted as a 17 vindication of Vanderbilt's arguments. 18 "Back in the late 1970s and 19 1980s, other talc companies were 20 distancing themselves from any deposit 21 that contained tremolite and of" -- "all, 22 of course, but Vanderbilt. They" -- 23 "Then they proceeded to poison the well." 24 Then the last e-mail is from</p>	<p>1 listed on here. So I guess I'm 2 missing the point of this. 3 What I stated is that my 4 research, animal studies, and OSHA 5 still to this day agree that 6 cleavage fragments do not pose the 7 same health risks as their 8 asbestiform counterparts. 9 BY MR. SMITH: 10 Q. Do you believe they pose any 11 health risk? 12 MR. FROST: Objection. 13 THE WITNESS: Well, 14 that's -- that's subjective. 15 Certainly with regard to 16 mesothelioma, no. There have been 17 many studies, including recent 18 ones from the EPA, that argue 19 against cleavage fragments as 20 causing cancer in animals. 21 BY MR. SMITH: 22 Q. What about ovarian cancer? 23 MR. FROST: Objection. 24 THE WITNESS: There in all</p>
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<p>1 Michelle -- I can't pronounce her last 2 name, from Rio Tinto Minerals, sent on 3 January 31st, 2008. And it said, "Dear 4 all, I agree with Rich's position." 5 So regarding cleavage 6 fragments and their ill health effects, 7 you had the employee of Luzenac, who was 8 head of regulatory affairs -- he was the 9 regulatory affairs manager, Rich 10 Zazenski, disagreeing with your position; 11 is that correct? 12 MR. FROST: Objection. I'll 13 just object to reading the e-mail 14 in, but... 15 THE WITNESS: He was 16 disagreeing with my position on? 17 BY MR. SMITH: 18 Q. On the ill health effects of 19 asbestos -- excuse me -- of cleavage 20 fragments on exposures. 21 MR. FROST: Objection. 22 THE WITNESS: Yeah, I'm not 23 sure what this correspondence is. 24 I have not -- I don't think I'm</p>	<p>1 of the experiments with cleavage 2 fragments in animals, ovarian 3 cancers have not developed. 4 BY MR. SMITH: 5 Q. Well, tell me what studies 6 have studied cleavage fragments in their 7 relation to ovarian cancer. 8 A. What I'm saying is that 9 cleavage fragments, by a variety of 10 routes, inhalation, intrapleural 11 injection, intraperitoneal, have not 12 developed -- have not resulted in the 13 development of ovarian cancers in 14 animals. Hundreds of -- 15 Q. Tell me the study that 16 studied cleavage fragments and their 17 relationship to ovarian cancer. 18 MR. FROST: Objection. 19 BY MR. SMITH: 20 Q. I want the specific study 21 that you're referencing. 22 A. That's not what I said. I'm 23 saying that cleavage fragments of a 24 variety of types have been assessed in</p>

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<p style="text-align: right;">Page 478</p> <p>1 lifetime studies with animals, including 2 studies with tremolite asbestos and 3 tremolite non-asbestos cleavage 4 fragments. 5 None of those studies have 6 ovarian cancer develop with either 7 asbestos other cleavage fragments. 8 Q. Have you -- do you know if 9 even ovarian cancer was looked for in 10 those studies? 11 MR. FROST: Objection. 12 THE WITNESS: These are 13 lifetime studies -- 14 BY MR. SMITH: 15 Q. Which studies? I need the 16 names of them. 17 MR. FROST: Objection. 18 THE WITNESS: Okay. Well, I 19 suggest that there -- many of them 20 are in my expert report. The ones 21 that I can think of are 22 Drs. Coffin at the EPA, recent 23 studies by Cyphert, C-Y-P-H-E-R-T, 24 who looked at ferro-actinolite</p>	<p style="text-align: right;">Page 480</p> <p>1 of them may be summarized in IARC. 2 BY MR. SMITH: 3 Q. All right. Let's move on. 4 Bullet Point 4. "Trace amounts of 5 cleavage fragments or other minerals may 6 be present in industrial and cosmetic 7 talcs have little or no chemical 8 biological reactivity." 9 We've gone through, I think, 10 some studies just a minute ago about 11 French government and NIOSH, and I'm 12 going to leave that bullet point alone. 13 A. Okay. 14 Q. Next bullet point. The 15 numerous -- "The results of numerous 16 epidemiological and experimental studies 17 assessing carcinogenic potential short 18 asbestos support the concept that short 19 fibers and cleavage fragments, even of 20 respirable dimensions, do not play a role 21 in the induction of tumors." 22 You have not looked at Longo 23 or Rigler's testing or any internal 24 documents about what asbestos has been</p>
<p style="text-align: right;">Page 479</p> <p>1 cleavage fragments. 2 BY MR. SMITH: 3 Q. And ovarian cancer? 4 A. What I'm telling you is that 5 people have not looked at ovarian cancer 6 and done studies and said, we're going to 7 expose animals and see whether they get 8 ovarian cancers. What they have looked 9 at have been lifetime studies in a 10 variety of organs and has not -- these 11 have not indicated that ovarian cancers 12 are a signature of cleavage fragments, 13 regardless of how much was instilled and 14 regardless of the route of administration 15 over the lifetime of the animals, all of 16 whom who were autopsied at death. 17 Q. Do you know any of those 18 that specifically looked at exposing 19 cleavage fragments and then -- to ovarian 20 tissue to determine whether they were 21 carcinogenic or had carcinogenic 22 properties to the ovaries? 23 MR. FROST: Objection. 24 THE WITNESS: I believe some</p>	<p style="text-align: right;">Page 481</p> <p>1 found in Baby Powder or Shower to Shower, 2 correct? 3 MR. FROST: Objection. 4 THE WITNESS: Yes. This is 5 not relevant to this, my 6 conclusions here. My conclusions 7 in terms of epidemiology and 8 experimental studies are based 9 upon the peer-reviewed scientific 10 literature and do not support the 11 concept that short fibers or 12 cleavage fragments play a role in 13 the induction of mesotheliomas or 14 ovarian cancers. 15 BY MR. SMITH: 16 Q. Well -- 17 A. And those are all referenced 18 within the report. 19 Q. Well, my point -- what I was 20 trying to get to, my second question is, 21 you don't know the fiber size or length 22 of asbestos found in these Baby Powder 23 bottles or Shower to Shower bottles. You 24 haven't seen the studies.</p>

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<p style="text-align: right;">Page 482</p> <p>1 MR. FROST: Objection to 2 form. 3 THE WITNESS: Again, sir, it 4 doesn't make any difference. All 5 of these studies and use of these 6 materials, regardless of their 7 source, were covered by cohort 8 studies with women looking at talc 9 exposures. And none of these have 10 shown convincing or statistical 11 increase in risk, and they haven't 12 indicated dose-response or 13 frequency effect. 14 So if they -- if there were 15 fibers there, such as asbestos 16 fibers in trace amounts or small 17 amounts, it still -- it wasn't 18 reflected at an increased 19 incidence of disease. 20 BY MR. SMITH: 21 Q. Fifth bullet point, 22 "Experimental studies demonstrate no 23 adverse effect levels from exposure to 24 certain concentrations of asbestos</p>	<p style="text-align: right;">Page 484</p> <p>1 effects document. These were summarized 2 in 1990. 3 Q. Well, you told me earlier 4 that you had not performed any studies on 5 those particular types of asbestos. 6 MR. FROST: Objection. 7 THE WITNESS: These are not 8 my studies. They are studies 9 where individuals have added 10 fibers of a variety of types of 11 asbestos to cells and have shown 12 that threshold levels exist below 13 which biological effects 14 indicative of tumor formation do 15 not occur. 16 BY MR. SMITH: 17 Q. As we discussed earlier, the 18 levels of exposure of each type of 19 asbestos in cosmetic-grade talc in terms 20 of human risk are outside your area of 21 expertise, correct? 22 MR. FROST: Objection. 23 THE WITNESS: Could you slow 24 down and --</p>
<p style="text-align: right;">Page 483</p> <p>1 fibers, indicating the existence of a 2 threshold for cancer causation below 3 which tumors do not develop." 4 None of the studies that you 5 cite for support of this opinion deal 6 with tremolite, anthophyllite, or 7 actinolite, correct? 8 MR. FROST: Objection. 9 THE WITNESS: I'd have to go 10 back and look at -- the 11 experimental studies that I'm 12 talking about are my own with 13 inhalation. And there are a 14 variety of studies with thresholds 15 in vitro that I summarize in a 16 2018 publication. 17 BY MR. SMITH: 18 Q. But they don't deal with 19 tremolite asbestos, anthophyllite 20 asbestos, or actinolite asbestos; is that 21 correct? 22 A. I'd have to go back and 23 look. Some of them might -- may have 24 dealt with tremolite in the health</p>	<p style="text-align: right;">Page 485</p> <p>1 BY MR. SMITH: 2 Q. As we discussed earlier, the 3 levels of exposure of each type of 4 asbestos in cosmetic-grade talc in terms 5 of human risk are outside of your area of 6 expertise, we talked about that earlier, 7 correct? 8 MR. FROST: Objection. 9 THE WITNESS: And, again, I 10 emphasize that it doesn't make any 11 difference what their levels would 12 be, in -- historically in talcum 13 powder if individuals using these 14 products did not develop ovarian 15 cancers. 16 BY MR. SMITH: 17 Q. All right. Let's go to -- 18 as far as the money that you've been 19 paid, how much -- much for J&amp;J have they 20 paid you totally, not just from the MDL? 21 How much have you made in 22 talc litigation, not just from the MDL, 23 do you know? 24 A. From J&amp;J, no, I would have</p>

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<p style="text-align: right;">Page 486</p> <p>1 no idea.</p> <p>2 Q. Can we get that, can you get</p> <p>3 that figure together and give it to your</p> <p>4 attorneys to give to us? Because I want</p> <p>5 the answer to that.</p> <p>6 A. Sure. What -- what</p> <p>7 information would you like?</p> <p>8 Q. How much you have made from</p> <p>9 Johnson &amp; Johnson in total, not just from</p> <p>10 the MDL, and how much money have you made</p> <p>11 since 2014 working in talc litigation.</p> <p>12 A. For Johnson &amp; Johnson?</p> <p>13 Okay.</p> <p>14 MR. FROST: You can follow</p> <p>15 up with a letter, we'll take it</p> <p>16 under advisement.</p> <p>17 THE WITNESS: Yeah. That's</p> <p>18 fine.</p> <p>19 MS. O'DELL: Thank you.</p> <p>20 THE WITNESS: Mm-hmm.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. You talked about Shih</p> <p>23 earlier. Is it your belief that this</p> <p>24 study tested Johnson &amp; Johnson talc?</p>	<p style="text-align: right;">Page 488</p> <p>1 BY MR. SMITH:</p> <p>2 Q. That's not -- it's</p> <p>3 nonresponsive. That's all I needed to</p> <p>4 know.</p> <p>5 A. Okay.</p> <p>6 Q. Have you spoken to Dr. Shih</p> <p>7 about this case?</p> <p>8 A. I have not.</p> <p>9 Q. Have you communicated with</p> <p>10 Dr. Ann Wiley about this case?</p> <p>11 A. Not this case, no.</p> <p>12 Q. When was the last time you</p> <p>13 spoke to her?</p> <p>14 A. Spoke to her? I would say</p> <p>15 probably last November at a meeting. A</p> <p>16 scientific meeting.</p> <p>17 Q. Have you discussed her depo</p> <p>18 with her?</p> <p>19 A. My depo?</p> <p>20 Q. Hers.</p> <p>21 A. No, I haven't read her depo.</p> <p>22 Q. Have you discussed your depo</p> <p>23 with her?</p> <p>24 A. No.</p>
<p style="text-align: right;">Page 487</p> <p>1 A. The studies that I saw by</p> <p>2 Shih --</p> <p>3 Q. It was an expert report.</p> <p>4 MR. FROST: Objection.</p> <p>5 THE WITNESS: It was an --</p> <p>6 let me emphasize. It was a</p> <p>7 scientific study where incipient,</p> <p>8 what are called pre-neoplastic</p> <p>9 lesions in the serous location --</p> <p>10 BY MR. SMITH:</p> <p>11 Q. Now, I'm -- Doctor, specific</p> <p>12 to my -- I'm sorry, I'm short on time. I</p> <p>13 need you to answer the question directly.</p> <p>14 Is it your belief that the</p> <p>15 study, the Shih study, the expert report</p> <p>16 that we discussed earlier that you said</p> <p>17 was a whiz-bang expert report, is it your</p> <p>18 belief that this -- this report tested</p> <p>19 J&amp;J talc?</p> <p>20 MR. FROST: Objection.</p> <p>21 THE WITNESS: I did not look</p> <p>22 at that information. These I</p> <p>23 believe were lesions from</p> <p>24 individuals with premalignant --</p>	<p style="text-align: right;">Page 489</p> <p>1 Q. Have you spoken or</p> <p>2 communicated with Dr. Laura Webb about</p> <p>3 this case?</p> <p>4 A. No, I have not.</p> <p>5 Q. She is a geologist here at</p> <p>6 the University of Vermont?</p> <p>7 A. Yes, I've met her before.</p> <p>8 Q. Have you communicated with</p> <p>9 Dr. Melinda Darby Dyar?</p> <p>10 A. I don't know that</p> <p>11 individual.</p> <p>12 Q. Heavy metals, nickels. What</p> <p>13 is the mechanism by which it causes</p> <p>14 cancer? Is it in connection?</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: Nickel?</p> <p>17 BY MR. SMITH:</p> <p>18 Q. Yes.</p> <p>19 A. It's particulate nickel.</p> <p>20 And no, it's generally through DNA</p> <p>21 damage. Nickel has a lot of effects on</p> <p>22 cells.</p> <p>23 Q. Can other heavy metals cause</p> <p>24 inflammation in tissues, such as</p>

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<p style="text-align: right;">Page 490</p> <p>1 chromium, cobalt, arsenic?</p> <p>2 A. Any material at a high</p> <p>3 enough concentration is going to cause</p> <p>4 inflammation, whether it's pathogenic or</p> <p>5 not.</p> <p>6 Q. Can heavy metals be</p> <p>7 cocarcinogens?</p> <p>8 MR. FROST: Objection.</p> <p>9 THE WITNESS: With cigarette</p> <p>10 smoke or other agents, I am sure</p> <p>11 there's data out there. I have</p> <p>12 not reviewed it. I can't give you</p> <p>13 an affirmative -- or a yes or no</p> <p>14 on that.</p> <p>15 BY MR. SMITH:</p> <p>16 Q. And Bob Glenn, I saw in some</p> <p>17 of your notes. He testified that "if</p> <p>18 there were fiber" -- "were a fiber of</p> <p>19 asbestos in talcum-based products, it</p> <p>20 would certainly provide a biologically</p> <p>21 plausible mechanism for increased lung</p> <p>22 disease, and that he suspected it would</p> <p>23 also have similar mechanism of disease in</p> <p>24 other tissues and organs."</p>	<p style="text-align: right;">Page 492</p> <p>1 Health Part A.</p> <p>2 Do you recall that?</p> <p>3 A. Yes. This is a paper that</p> <p>4 was presented at a conference of which</p> <p>5 the journal published the conference</p> <p>6 paper. So it wouldn't be through a --</p> <p>7 let's say a review -- review process as</p> <p>8 would -- I would have done for a</p> <p>9 high-impact journal. It was a --</p> <p>10 (Document marked for</p> <p>11 identification as Exhibit</p> <p>12 Mossman-46.)</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Well, here is the impact</p> <p>15 factor during the year that you published</p> <p>16 Hillegass, which was 1.637. Do you see</p> <p>17 that? Look at the screen.</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: Yeah, that --</p> <p>20 that could have been. This was a</p> <p>21 journal that was used by the EPA</p> <p>22 scientists for meetings, and as I</p> <p>23 emphasize, the original data in</p> <p>24 that paper was --</p>
<p style="text-align: right;">Page 491</p> <p>1 Do you agree with him?</p> <p>2 MR. FROST: Objection.</p> <p>3 THE WITNESS: I believe that</p> <p>4 was a misquote in Dr. Zelikoff's</p> <p>5 report.</p> <p>6 BY MR. SMITH:</p> <p>7 Q. All right. Let's go to your</p> <p>8 report real quick.</p> <p>9 You stated -- there was a</p> <p>10 criticism of Dr. Saed about the</p> <p>11 low-impact journal. You said you put his</p> <p>12 impact journal figures out about his</p> <p>13 publication. Do you recall that? And it</p> <p>14 was 2.548; is that right?</p> <p>15 A. No, I didn't put his impact</p> <p>16 figure out there. I provided a table of</p> <p>17 impact factors.</p> <p>18 Q. Okay. And regardless it's</p> <p>19 in your report, correct?</p> <p>20 A. I have a table of impact</p> <p>21 factors, yes, in my report.</p> <p>22 Q. Okay. And your -- the</p> <p>23 Hillegass study was published in the</p> <p>24 Journal of Toxicology and Environmental</p>	<p style="text-align: right;">Page 493</p> <p>1 MR. SMITH: How much time I</p> <p>2 got?</p> <p>3 THE WITNESS: -- reported by</p> <p>4 Dr. Shukla.</p> <p>5 BY MR. SMITH:</p> <p>6 Q. Okay.</p> <p>7 A. So this was a conference</p> <p>8 paper.</p> <p>9 Q. I want to go to your report.</p> <p>10 And on Page 10, it says, "Anatomy of the</p> <p>11 Female Reproductive Parts And Barriers To</p> <p>12 Particles."</p> <p>13 It says, "As illustrated in</p> <p>14 Figure 3 below, the extended genitalia</p> <p>15 are the first line of defense in that</p> <p>16 'the skin constitutes a relatively</p> <p>17 impenetrable barrier to most</p> <p>18 microorganisms unless breached by injury</p> <p>19 such as abrasion or burning.'"</p> <p>20 You believe that the female</p> <p>21 reproductive tract, there's an</p> <p>22 impenetrable barrier?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: I think --</p>

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<p style="text-align: right;">Page 494</p> <p>1 what I'm emphasizing here, and 2 this is a book that actually has 3 been used to tutor individuals in 4 basic pathology, that the skin is 5 an impenetrable barrier to 6 particulate matter. 7 BY MR. SMITH: 8 Q. Okay. Let's go to the next 9 page. It talks about "ovarian cancer" -- 10 "cancers develop from epithelial cells 11 that line the ovaries and oviducts, 12 fallopian tubes. These structures are 13 surrounded by a protected fibrous 14 capsule." 15 What fibrous capsule is 16 around human ovarian -- ovaries? 17 MR. FROST: Objection. 18 THE WITNESS: So the ovarian 19 epithelium is lined by something 20 called the submucosal or the 21 interstitium. And that's 22 comprised of blood vessels and 23 fibers, meaning fibers from the 24 stroma. So this is called a</p>	<p style="text-align: right;">Page 496</p> <p>1 or not he used fallopian tubes cells in 2 his study? 3 A. It may have been one of the 4 lines that he looked at, but whether they 5 were normal or whether it was his one 6 normal line -- 7 Q. Do you know? 8 A. -- it is unclear. No. 9 Q. Did you have -- do you have 10 the capability of replicating Dr. Saed's 11 study if you wanted to try to replicate 12 it? 13 MR. FROST: Objection. 14 THE WITNESS: I wouldn't 15 want to. 16 BY MR. SMITH: 17 Q. Could you replicate it? 18 MR. FROST: Objection. 19 BY MR. SMITH: 20 Q. Could you do it? 21 A. I wouldn't do it the same 22 way he did it. 23 Q. I don't -- that's not what 24 I'm asking. I'm asking, could you</p>
<p style="text-align: right;">Page 495</p> <p>1 protective fibrous capsule. 2 Similar to the -- the lung 3 epithelium, which has a supportive 4 fibrous capsule under it, called 5 the interstitium. It's sometimes 6 called the stroma. 7 BY MR. SMITH: 8 Q. Do you know what -- we did 9 the conversion charts of -- well, do you 10 know the concentration levels that 11 Dr. Saed used in his study? 12 A. That was very difficult to 13 discern. 14 Q. Okay. Do you know -- did 15 you know -- did you see if Dr. Saed used 16 normal epithelial cells? 17 A. If he did, the -- 18 Q. Do you know if he did or 19 not? 20 MR. FROST: Objection. 21 THE WITNESS: I doubt very 22 much he did. 23 BY MR. SMITH: 24 Q. Okay. Do you know whether</p>	<p style="text-align: right;">Page 497</p> <p>1 replicate it if I asked you to do it? 2 MR. FROST: Objection. 3 BY MR. SMITH: 4 Q. Do you have the ability to 5 do it? 6 A. As he did, there are so many 7 flaws in his methodology, I just don't 8 know where to start. I mean, if we had 9 two hours, fine. 10 Q. My question is very simple. 11 If you had the -- do you have the 12 capability of replicating his study? Yes 13 or no? 14 MR. FROST: Objection. 15 THE WITNESS: I wouldn't 16 want to. And it has -- when you 17 say replicate -- 18 BY MR. SMITH: 19 Q. If you just followed exactly 20 what he did in his study, could you do 21 exactly what he did if I told you to do 22 exactly what he did in his study? 23 A. I wouldn't -- I wouldn't do 24 it.</p>



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<p style="text-align: right;">Page 498</p> <p>1 Q. That's not what I'm asking. 2 I'm saying could you? Do you have the 3 ability to do it? 4 A. As he did it? 5 Q. Again, I -- do you have the 6 ability to replicate his study? Yes or 7 no? 8 MR. FROST: Objection. 9 THE WITNESS: Based upon how 10 he describes it, no, there's not 11 enough detail there. 12 BY MR. SMITH: 13 Q. Okay. 14 A. And there's so many flaws. 15 Q. Did you attempt to replicate 16 his study and -- did you attempt to 17 replicate his study? 18 A. You mean I would actually 19 perform that study -- 20 Q. Yep. 21 A. -- as he did? 22 Q. Yep. 23 A. No. I wouldn't bother, 24 because it doesn't tell you anything.</p>	<p style="text-align: right;">Page 500</p> <p>1 THE WITNESS: They are 2 Vermont and Italian talc sources 3 from which Johnson's material may 4 have come from. 5 BY MR. SMITH: 6 Q. May have? 7 A. I don't know the details on 8 that. 9 Q. Okay. All right. Next 10 page, Page 29. You have Karageorgi 11 listed. And it says, "This group studied 12 the possible relationship between use of 13 talcum powder and endometrial cancer." 14 Do you see that? 15 A. Yes. 16 Q. And you say, "This group 17 found no statistical association and 18 concluded that future studies were 19 needed." You're saying that the 20 Karageorgi found no statistical 21 association between talcum powder and 22 endometrial cancer risk? Is that what 23 the conclusion of this study was? 24 A. I'd have to go back and look</p>
<p style="text-align: right;">Page 499</p> <p>1 Q. You have a statement on Page 2 28. You have two studies cited for there 3 not being talc -- I mean, excuse me, 4 asbestos in Baby Powder. And that is 5 Boundy and Pira. 6 Do you see that on Page 28, 7 first bullet point? 8 A. These are studies on the 9 workers that were exposed to these talcs. 10 Q. Is that your basis that 11 there is not asbestos in Baby Powder or 12 Shower to Shower? 13 MR. FROST: Objection to 14 form. 15 THE WITNESS: It was stated 16 in these industrial talcs that 17 they were not associated with 18 asbestos contamination. 19 BY MR. SMITH: 20 Q. Those are industrial talcs, 21 not cosmetic-grade talcs. You understand 22 Baby Powder and Shower to Shower are 23 cosmetic-grade talcs, ma'am, don't you? 24 MR. FROST: Objection.</p>	<p style="text-align: right;">Page 501</p> <p>1 at it. It dealt with endometrial 2 cancers. I'd have to go back and review 3 it. 4 Dr. Saed stated it had -- 5 that it studied ovarian cancer, and that 6 was not the case. 7 Q. That's not my question to 8 you, Doctor. My question to you is, did 9 the study conclude that there was no 10 statistical association found between 11 talcum powder use and endometrial cancer? 12 MR. FROST: Objection. 13 THE WITNESS: It -- I 14 believe that it stated there might 15 be a risk, but future studies were 16 merited. I don't recall it 17 without looking at the -- 18 (Document marked for 19 identification as Exhibit 20 Mossman-47.) 21 BY MR. SMITH: 22 Q. This is the next numbered 23 exhibit, 47. 24 A. -- conclusions.</p>

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<p>1 Q. And this is that study?</p> <p>2 A. Okay.</p> <p>3 Q. And we go to conclusions</p> <p>4 right at the first of the abstract. "Our</p> <p>5 results suggest that perineal talcum</p> <p>6 powder use increases the risk of</p> <p>7 endometrial cancer, particularly around</p> <p>8 postmenopausal women."</p> <p>9 Attach that as Exhibit 47.</p> <p>10 MR. FROST: Objection. I</p> <p>11 don't know that there's a question</p> <p>12 there.</p> <p>13 BY MR. SMITH:</p> <p>14 Q. Well, obviously, that's</p> <p>15 different than what you put in your</p> <p>16 report on Page 29, correct?</p> <p>17 A. The reason I put it in my</p> <p>18 report is that Dr. Saed said that this is</p> <p>19 a study linking perineal use of talcum</p> <p>20 powder to ovarian cancers. That is not</p> <p>21 what Dr. Karageorgi studied here. He</p> <p>22 looked at endometrial cancer risk.</p> <p>23 I believe here, and I'd have</p> <p>24 to look, but I see it now. In the</p>	<p>1 results were at the low level of</p> <p>2 talc exposure and resulted in no</p> <p>3 significant increases; therefore,</p> <p>4 you didn't get a time-dependent or</p> <p>5 dose-dependent increase --</p> <p>6 BY MR. SMITH:</p> <p>7 Q. Well, I don't want to go</p> <p>8 back over it --</p> <p>9 A. -- in gene expression.</p> <p>10 Q. -- but you don't know if you</p> <p>11 got a time or dose-dependent at the</p> <p>12 higher concentrations because you didn't</p> <p>13 test it.</p> <p>14 A. It doesn't make a</p> <p>15 difference.</p> <p>16 Q. You didn't test it at 24</p> <p>17 hours, did you?</p> <p>18 MR. FROST: Objection.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Did you? Yes or no?</p> <p>21 MR. FROST: Objection.</p> <p>22 THE WITNESS: Low</p> <p>23 concentrations, yes, we did.</p> <p>24 BY MR. SMITH:</p>
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<p>1 abstract, it was a borderline increase in</p> <p>2 risk, and it was not related to dose or</p> <p>3 frequency. And he concludes that future</p> <p>4 studies need to be done to make</p> <p>5 conclusions.</p> <p>6 Q. On Page 30, on the -- one,</p> <p>7 two, three, four -- fourth bullet point,</p> <p>8 starting "On Page 12," of your report.</p> <p>9 It says, "On page 12." It goes down and</p> <p>10 says, "He does not acknowledge that ATF3</p> <p>11 was characterized as an inhibitor of</p> <p>12 inflammation in our studies, and unlike</p> <p>13 asbestos, no changes in gene expression</p> <p>14 were observed at 24 hours in mesothelial</p> <p>15 or ovarian epithelial after exposure to</p> <p>16 talc."</p> <p>17 That is not true. They were</p> <p>18 not done at 24 at high concentrations,</p> <p>19 were they?</p> <p>20 MR. FROST: Objection.</p> <p>21 BY MR. SMITH:</p> <p>22 Q. Were they?</p> <p>23 MR. FROST: Objection.</p> <p>24 THE WITNESS: The 24-hour</p>	<p>1 Q. High concentration. The</p> <p>2 higher concentration, did you?</p> <p>3 MR. FROST: Objection.</p> <p>4 THE WITNESS: We didn't look</p> <p>5 at asbestos or talc at high</p> <p>6 concentrations.</p> <p>7 MR. FROST: How are we doing</p> <p>8 on time?</p> <p>9 THE VIDEOGRAPHER: You've</p> <p>10 got a minute left.</p> <p>11 BY MR. SMITH:</p> <p>12 Q. Okay.</p> <p>13 And you talk about</p> <p>14 Dr. Saed's lack of knowledge about</p> <p>15 ovarian cancer. Have you seen the</p> <p>16 publications that he's published on,</p> <p>17 Doctor?</p> <p>18 MR. FROST: Objection.</p> <p>19 THE WITNESS: Do you want me</p> <p>20 to answer that?</p> <p>21 Yes, the few he has which</p> <p>22 are not in high impact journals</p> <p>23 and not what they say they are.</p> <p>24 BY MR. SMITH:</p>

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<p style="text-align: right;">Page 506</p> <p>1 Q. Let me tell you what -- I'll</p> <p>2 tell you what, I take exception to you</p> <p>3 laughing and your sarcasm about Dr. Saed.</p> <p>4 I just want to tell you I take --</p> <p>5 A. Well --</p> <p>6 Q. -- I think that is low rent</p> <p>7 and classless.</p> <p>8 But my question to you is,</p> <p>9 do you know if he's published any</p> <p>10 peer-reviewed literature prior to</p> <p>11 litigation on oxidative stress and</p> <p>12 inflammation and it leading to ovarian</p> <p>13 cancer? Do you know at this time?</p> <p>14 A. He's had --</p> <p>15 MR. FROST: Objection.</p> <p>16 THE WITNESS: He's had a few</p> <p>17 papers on chemo resistance in</p> <p>18 ovarian cancer cells.</p> <p>19 BY MR. SMITH:</p> <p>20 Q. Have you had any prior</p> <p>21 publications in that area?</p> <p>22 MR. FROST: Objection.</p> <p>23 BY MR. SMITH:</p> <p>24 Q. Yourself?</p>	<p style="text-align: right;">Page 508</p> <p>1</p> <p>2 CERTIFICATE</p> <p>3</p> <p>4</p> <p>5 I HEREBY CERTIFY that the</p> <p>6 witness was duly sworn by me and that the</p> <p>7 deposition is a true record of the</p> <p>8 testimony given by the witness.</p> <p>9</p> <p>10 It was requested before</p> <p>11 completion of the deposition that the</p> <p>12 witness, BROOKE T. MOSSMAN, M.S., Ph.D.,</p> <p>13 have the opportunity to read and sign the</p> <p>14 deposition transcript.</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>13 MICHELLE L. GRAY,</p> <p>14 A Registered Professional</p> <p>15 Reporter, Certified Shorthand</p> <p>16 Reporter, Certified Realtime</p> <p>17 Reporter and Notary Public</p> <p>18 Dated: April 9, 2019</p> <p>19 (The foregoing certification</p> <p>20 of this transcript does not apply to any</p> <p>21 reproduction of the same by any means,</p> <p>22 unless under the direct control and/or</p> <p>23 supervision of the certifying reporter.)</p> <p>24</p>
<p style="text-align: right;">Page 507</p> <p>1 A. In chemo resistance, no.</p> <p>2 MR. FROST: How are we</p> <p>3 doing? We done?</p> <p>4 All right. Great. Let me</p> <p>5 just consult with my colleague,</p> <p>6 but I have a feeling we're done.</p> <p>7 Yeah, we're done.</p> <p>8 THE VIDEOGRAPHER: This</p> <p>9 concludes today's deposition.</p> <p>10 We're going off the record. The</p> <p>11 time is 5:55.</p> <p>12 (Excused.)</p> <p>13 (Deposition concluded at</p> <p>14 approximately 5:55 p.m.)</p> <p>15 - - -</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 509</p> <p>1 INSTRUCTIONS TO WITNESS</p> <p>2</p> <p>3 Please read your deposition</p> <p>4 over carefully and make any necessary</p> <p>5 corrections. You should state the reason</p> <p>6 in the appropriate space on the errata</p> <p>7 sheet for any corrections that are made.</p> <p>8 After doing so, please sign</p> <p>9 the errata sheet and date it.</p> <p>10 You are signing same subject</p> <p>11 to the changes you have noted on the</p> <p>12 errata sheet, which will be attached to</p> <p>13 your deposition.</p> <p>14 It is imperative that you</p> <p>15 return the original errata sheet to the</p> <p>16 deposing attorney within thirty (30) days</p> <p>17 of receipt of the deposition transcript</p> <p>18 by you. If you fail to do so, the</p> <p>19 deposition transcript may be deemed to be</p> <p>20 accurate and may be used in court.</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>

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<div style="text-align: center;">- - - - - E R R A T A - - - - -</div> <p>PAGE LINE CHANGE</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p> <p>REASON: _____</p>	<div style="text-align: center;">LAWYER'S NOTES</div> <p>PAGE LINE</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>
<div style="text-align: right; padding-right: 20px;">Page 511</div> <p>ACKNOWLEDGMENT OF DEPONENT</p> <p>I, _____, do</p> <p>hereby certify that I have read the foregoing pages, 1 - 512, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.</p> <p>_____</p> <p>BROOKE T. MOSSMAN, M.S., Ph.D. DATE</p> <p>Subscribed and sworn to before me this</p> <p>_____ day of _____, 20____.</p> <p>My commission expires: _____</p> <p>_____</p> <p>Notary Public</p>	

<b>A</b>				
<b>A-N-S-E-S</b>	<b>access</b> 189:13	<b>actions</b> 315:11	463:15	<b>agents</b> 54:10,23
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363:23	<b>21st</b> 23:15	<b>29</b> 308:2,9	456:18	<b>45</b> 73:12,15
<b>2006</b> 93:2	159:20	311:10,17	<b>334</b> 2:10	216:23 288:9
218:21 220:18	<b>22</b> 226:6,20	394:13 500:10	<b>34</b> 353:6 355:3	470:19
<b>2007</b> 198:1	227:3,6	502:16	409:23 413:6	<b>463</b> 10:15
336:2 345:19	<b>222</b> 7:15	<b>299</b> 8:6	<b>346</b> 8:21	<b>463-2400</b> 3:14
<b>2008</b> 236:13	<b>226</b> 7:11	<b>2A</b> 419:19	<b>35</b> 192:9,13	<b>465</b> 10:17
237:6 253:24	<b>23</b> 211:21 227:7	<b>2D</b> 421:15,17	353:11 377:7	<b>47</b> 289:18
256:17 291:1	237:15	<b>2s</b> 423:5	427:3	501:23 502:9
308:9 323:1,1	<b>233</b> 3:18		<b>352</b> 9:6	<b>470</b> 10:20
336:2 471:23	<b>236</b> 389:9		<b>353</b> 9:9,13	<b>49</b> 31:22 34:3
475:3	<b>237</b> 7:13		<b>358</b> 9:16	<b>492</b> 11:6
<b>2009</b> 235:9	<b>24</b> 47:20 48:14	<b>3</b> 16:16 59:1,15	<b>36</b> 412:12	
264:7 275:17	85:6 222:11	90:7,15 105:14	<b>36104</b> 2:9	<b>5</b>
353:14 413:14	226:11,23	111:9 217:20	<b>366</b> 9:18	<b>5</b> 62:14 77:5
415:17	227:1 262:23	378:10 400:11	<b>37</b> 359:11	160:15 288:1
<b>2010</b> 120:16	263:10 369:7	401:3 407:20	<b>371-7008</b> 3:9	294:7 303:8
121:6 122:24	369:21 370:7	410:4 433:6	<b>38</b> 366:8	416:10 418:17
151:24 152:2,5	370:10 371:16	467:13 493:14	<b>387</b> 104:10	424:10 446:17
152:12,16,18	372:12,22	<b>3,000</b> 386:9,9	<b>388</b> 9:22	<b>5,000</b> 425:13
176:17 177:9	373:6,11,17	<b>3.1</b> 295:7	<b>39</b> 285:15 288:1	<b>5/8/09</b> 9:13
181:19 343:23	374:7 391:6,9	<b>3/15/19</b> 10:11	295:6 416:13	<b>5:55</b> 507:11,14
463:15	392:16 396:6	<b>30</b> 46:5 49:10	421:22	<b>50</b> 68:18 188:14
<b>2011</b> 366:15	403:15 416:17	69:19 74:20	<b>39157</b> 2:5	<b>501</b> 11:8
<b>2012</b> 120:23	416:20 418:13	302:21 312:4,8		<b>512</b> 511:6
220:16	418:21,24	369:16 374:5	<b>4</b>	<b>53</b> 93:14
		375:9,21 376:7		

<b>55</b> 133:6	353:14 430:2			
<b>550</b> 76:3	<b>80s</b> 180:11			
<b>58</b> 4:19	<b>81</b> 356:16 381:5			
	<b>82</b> 5:8			
<b>6</b>	<b>83</b> 5:10 23:13			
<b>6</b> 9:22 34:4	24:12			
79:14 323:4,23	<b>85</b> 61:22 62:1			
324:6 353:22	402:13,19			
389:2 410:20	<b>86</b> 62:1 296:11			
421:21,22	297:16 298:3			
<b>600</b> 3:4	299:3			
<b>601</b> 2:5	<b>87</b> 55:16 62:1			
<b>60606</b> 3:19	<b>877.370.3377</b>			
<b>60s</b> 180:11	1:20			
<b>62</b> 7:6 91:13	<b>88</b> 5:12			
196:1,19	<b>8th</b> 13:6			
<b>624-6307</b> 3:19				
<b>65</b> 6:12 69:6	<b>9</b>			
121:7,11,12,18	<b>9</b> 83:1 89:7			
122:2 195:4	508:15			
<b>66</b> 127:9,13,20	<b>9:12</b> 1:15 13:7			
<b>6950</b> 3:18	<b>90</b> 383:2			
	<b>90s</b> 180:12			
<b>7</b>	212:14			
<b>7</b> 198:1 413:19	<b>917.591.5672</b>			
469:5	1:20			
<b>70</b> 268:22	<b>92</b> 5:14 29:18,20			
269:22 270:24	192:9,13,19			
271:1	193:11			
<b>70s</b> 180:11	<b>92660</b> 2:14			
<b>720-1288</b> 2:14	<b>949</b> 2:14			
<b>75</b> 46:8 68:19	<b>952-1422</b> 2:5			
355:5 356:10	<b>96</b> 5:16 338:5			
356:11,16	339:7			
357:6 378:20	<b>973)549.7106</b>			
380:21 386:4	3:5			
388:4 400:13	<b>975</b> 3:13			
419:14	<b>98</b> 176:4			
<b>76</b> 4:21 192:19	<b>99</b> 338:4			
193:11,17				
<b>78</b> 27:1,12				
<b>79</b> 5:6				
<b>8</b>				
<b>8</b> 1:10 24:17				
44:12 83:24				
323:4,23 324:6				

# Exhibit C

# Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer

Reproductive Sciences  
1-10  
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DOI: 10.1177/1933719119831773  
journals.sagepub.com/home/rsx  


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## Abstract

Genital use of talcum powder and its associated risk of ovarian cancer is an important controversial topic. Epithelial ovarian cancer (EOC) cells are known to manifest a persistent prooxidant state. Here we demonstrated that talc induces significant changes in key redox enzymes and enhances the prooxidant state in normal and EOC cells. Using real-time reverse transcription polymerase chain reaction and enzyme-linked immunosorbent assay, levels of CA-125, caspase-3, nitrate/nitrite, and selected key redox enzymes, including myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GSR), were determined. TaqMan genotype analysis utilizing the QuantStudio 12K Flex was used to assess single-nucleotide polymorphisms in genes corresponding to target enzymes. Cell proliferation was determined by MTT proliferation assay. In all talc-treated cells, there was a significant dose-dependent increase in prooxidant iNOS, nitrate/nitrite, and MPO with a concomitant decrease in antioxidants CAT, SOD, GSR, and GPX ( $P < .05$ ). Remarkably, talc exposure induced specific point mutations that are known to alter the activity in some of these key enzymes. Talc exposure also resulted in a significant increase in inflammation as determined by increased tumor marker CA-125 ( $P < .05$ ). More importantly, talc exposure significantly induced cell proliferation and decreased apoptosis in cancer cells and to a greater degree in normal cells ( $P < .05$ ). These findings are the first to confirm the cellular effect of talc and provide a molecular mechanism to previous reports linking genital use to increased ovarian cancer risk.

## Keywords

talc, epithelial ovarian cancer, oxidative stress, single-nucleotide polymorphism, cell proliferation

## Introduction

Ovarian cancer is the most lethal gynecologic malignancy and ranks fifth in cancer deaths among women diagnosed with cancer.<sup>1</sup> Epithelial ovarian cancer (EOC) has long been considered a heterogeneous disease with respect to histopathology, molecular biology, and clinical outcome.<sup>1,2</sup> Although surgical techniques and treatments have advanced over the years, the prognosis of EOC remains poor, with a 5-year survival rate of 50% in advanced stage.<sup>2</sup> This is largely due to the lack of early warning symptoms and screening methods and the development of chemoresistance.<sup>1,2</sup> Moreover, ovarian cancer is known to be associated with germline mutations in the *BRCA1* or *BRCA2* genes, but with a rate of only 20 % to 40%, suggesting the presence of other unknown mutations in other predisposition genes.<sup>3</sup> Additional genetic variations including single-nucleotide polymorphisms (SNPs) have been hypothesized to act as low to moderate penetrant alleles that contribute to ovarian cancer risk.<sup>3,4</sup>

The pathophysiology of EOC is not fully understood but has been strongly associated with inflammation and the resultant

oxidative stress.<sup>5</sup> We have previously characterized EOC cells to manifest a persistent prooxidant state as evident by the upregulation of key oxidants and downregulation of key antioxidants, which is further enhanced in chemoresistant EOC cells.<sup>6</sup> The expression of key prooxidant/inflammatory enzymes such as inducible nitric oxide synthase (iNOS), nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase, and myeloperoxidase (MPO), as well as an increase in nitric oxide (NO) levels, was increased in EOC tissues and cells.<sup>6</sup> Additionally, we have shown that EOC cells manifest lower apoptosis, which

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was markedly induced by inhibiting iNOS, indicating a strong link between apoptosis and NO/iNOS pathways in these cells.<sup>6</sup>

The cellular redox balance is maintained by key antioxidants including catalase (CAT), superoxide dismutase (SOD), or by glutathione peroxidase (GPX) coupled with glutathione reductase (GSR).<sup>5</sup> Other important scavengers include thioredoxin coupled with thioredoxin reductase, and glutaredoxin, which utilizes glutathione (GSH) as a substrate.<sup>7</sup> We have previously reported that a genotype switch in key antioxidants is a potential mechanism leading to the acquisition of chemoresistance in EOC cells.<sup>7</sup> We have studied the effects of genetic polymorphisms in key redox genes on the acquisition of the oncogenic phenotype in EOC cells, including genes that control the levels of cellular reactive oxygen species and oxidative damage and SNPs for genes involved in carcinogen metabolism (detoxification and/or activation), antioxidants, and DNA repair pathways.<sup>4,6</sup> Several function-altering SNPs have been identified in key antioxidants, including CAT, GPX, GSR, and SOD.<sup>4</sup>

Several studies have suggested the possible association between genital use of talcum powder and risk of EOC.<sup>7-12</sup> Association between the use of cosmetic talc in genital hygiene and ovarian cancer was first described in 1982 by Cramer et al, and many subsequent studies supported this finding.<sup>7-12</sup> Talc and asbestos are both silicate minerals; the carcinogenic effects of asbestos have been extensively studied and documented in the medical literature.<sup>7-12</sup> Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate a similar inflammatory response.<sup>7</sup> The objective of this study was to determine the effects of talcum powder on the expression of key redox enzymes, CA-125 levels, and cell proliferation and apoptosis in normal and EOC cells.

## Material and Methods

### Cell Lines

Ovarian cancer cells SKOV-3 (ATCC), A2780 (Sigma Aldrich, St Louis, Missouri), and TOV112D (a kind gift from Gen Sheng Wu at Wayne State University, Detroit, Michigan) and normal cells human macrophages (EL-1; ATCC, Manassas, Virginia), human primary normal ovarian epithelial cells (Cell Biologics, Chicago, Illinois), human ovarian epithelial cells (HOSEpiC; ScienCell Research Laboratories, Inc, Carlsbad, California), and immortalized human fallopian tube secretory epithelial cells (FT33; Applied Biological Materials, Richmond, British Columbia, Canada) were used. All cells were grown in media and conditions following manufacturer's protocol. EL-1 cells were grown in IMDM media (ATCC) supplemented with 0.1 mM hypoxanthine and 0.1 mM thymidine solution (H-T, ATCC) and 0.05 mM  $\beta$ -mercaptoethanol. SKOV-3 EOC cells were grown in HyClone McCoy's 5A medium (Fisher Scientific, Waltham, Massachusetts), A2780 EOC cells were grown in HyClone RPMI-1640 (Fisher Scientific), and both TOV112D EOC cells were grown in MCDB105

(Cell Applications, San Diego, California) and Medium 199 (Fisher Scientific; 1:1). All media were supplemented with fetal bovine serum (Innovative Research, Novi, Michigan) and penicillin/streptomycin (Fisher Scientific), per their manufacturer specifications. Human primary normal ovarian epithelial cells were grown in complete human epithelial cell medium (Cell Biologics).

### Treatment of Cells

Talcum baby powder (Johnson & Johnson, New Brunswick, NJ, #30027477, Lot#13717RA) was dissolved in dimethyl sulfoxide (DMSO; Sigma Aldrich) at a concentration of 500 mg in 10 mL and was filtered with a 0.2  $\mu$ m syringe filter (Corning). Sterile DMSO was used as a control for all treatments. Cells were seeded in 100-mm cell culture dishes ( $3 \times 10^6$ ) and were treated 24 hours later with 5, 20, or 100  $\mu$ g/mL of talc for 72 hours. Cell pellets were collected for RNA, DNA, and protein extraction. Cell culture media were collected for CA-125 analysis by enzyme-linked immunosorbent assay (ELISA).

### Real-Time Reverse Transcription Polymerase Chain Reaction

Total RNA was extracted from all cells using the RNeasy mini kit (Qiagen, Valencia, California). Measurement of the amount of RNA in each sample was performed using a Nanodrop spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts). A 20  $\mu$ L complementary DNA reaction volume containing 0.5  $\mu$ g RNA was prepared using the SuperScript VILO Master Mix Kit (Life Technologies, Carlsbad, California). Optimal oligonucleotide primer pairs were selected for each target using Beacon designer (Premier Biosoft, Inc; Table 1). Quantitative reverse transcription polymerase chain reaction (RT-PCR) was performed using the EXPRESS SYBR GreenER qPCR supermix kit (Life Technologies) and the Cepheid 1.2f detection system (Sunnyvale, CA) previously described.<sup>6</sup> Standards with known concentrations and lengths were designed specifically for  $\beta$ -actin (79 bp), CAT (105 bp), NOS2 (89 bp), GSR (103 bp), GPX1 (100 bp), MPO (79 bp), and SOD3 (84 bp), allowing for construction of a standard curve using a 10-fold dilution series.<sup>6</sup> All samples were normalized to  $\beta$ -actin. A final melting curve analysis was performed to demonstrate specificity of the PCR product.

### Protein Detection

Cell pellets were lysed utilizing cell lysis buffer (20 mM Tris-HCl [pH 7.5], 150 mM NaCl, 1 mM Na<sub>2</sub>EDTA, 1 mM EGTA, 1% Triton, 2.5 sodium pyrophosphate, 1 mM  $\beta$ -glycerophosphate, 1 mM Na<sub>3</sub>VO<sub>4</sub>, 1  $\mu$ g/mL leupeptin) containing a cocktail of protease inhibitors. Samples were centrifuged at 13 000 rpm for 10 minutes at 4 C. Total protein concentration of cell lysates from control and talc-treated cells was measured with the Pierce BCA protein assay kit (Thermo Scientific, Rockford, Illinois).



**Table 1.** Real-Time RT-PCR Oligonucleotide Primers.

Accession Number	Gene	Sense (5'-3')	Antisense (3'-5')	Amplicon (bp)	Annealing Time (seconds) and Temperature (°C)
NM_001101	<i>β-actin</i>	ATGACTTAGTTGCGTTACAC	AATAAAGCCATGCCAATCTC	79	10, 64
NM_001752	<i>CAT</i>	GGTTGAACAGATAGCCTTC	CGGTGAGTGTGAGGATAG	105	10, 63
NM_003102	<i>SOD3</i>	GTGTTCTGCTGCTCCT	TCCGCCGAGTCAGAGTTG	84	60, 64
NM_000637	<i>GSR</i>	TCACCAAGTCCCATATAGAAATC	TGTGGCGATCAGGATGTG	116	10, 63
NM_000581	<i>GPX1</i>	GGACTACACCCAGATGAAC	GAGCCCTTGCGAGGTGTAG	91	10, 66
NM_000625	<i>NOS2</i>	GAGGACCACATCTACCAAGGAGGAG	CCAGGCAGGCGGAATAGG	89	30, 59
NM_000250	<i>MPO</i>	CACTTGTATCCTCTGGTTCTTCAT	TCTATATGCTTCTCACGCCTAGTA	79	60, 63

Abbreviation: RT-PCR, reverse transcription polymerase chain reaction.

### Detection of Protein/Activity by ELISA

The following ELISA kits were used (Cayman Chemical, Ann Arbor, Michigan): CAT, SOD, GSR, GPX, and MPO. Nitrite ( $\text{NO}_2^-$ )/nitrate ( $\text{NO}_3^-$ ) were determined spectrophotometrically by Griess assay as previously reported.<sup>6</sup> CA-125 protein levels were measured in cell media by ELISA (Ray Biotech, Norcross, Georgia).

### TaqMan SNP Genotyping Assay

DNA was isolated utilizing the EZ1 DNA tissue kit (Qiagen) for EOC cells. The TaqMan SNP genotyping assay set (Applied Biosystems, Carlsbad, California; NCBI dbSNP genome build 37, MAF source 1000 genomes) was used to genotype the SNPs (Table 1). The Applied Genomics Technology Center (AGTC, Wayne State University) performed these assays. Analysis was done utilizing the QuantStudio 12 K Flex real-time PCR system (Applied Biosystems).

### Cell Proliferation and Apoptosis

Cell proliferation was assessed with the TACS MTT cell proliferation assay (Trevigen, Gaithersburg, Maryland) after treatment with talc (100  $\mu\text{g/mL}$ ) for 24 hours. The Caspase-3 Colorimetric Activity Assay Kit (Chemicon, Temecula, California) was used to determine levels of caspase-3 activity after treatment of normal and EOC cells with various doses of talc as previously described.<sup>6</sup> Equal concentrations of cell lysate were used. The assay is based on spectrophotometric detection of the chromophore p-nitroaniline (pNA) after cleavage from the labeled substrate DEVD-pNA. The free pNA can be quantified using a spectrophotometer or a microtiter plate reader at 405 nm. Comparison of the absorbance of pNA from an apoptotic sample with its control allows determination of the percentage increase in caspase-3 activity.

### Statistical Analysis

Normality was examined using the Kolmogorov-Smirnov test and by visual inspection of quantile-quantile plots. Because most of the data were not normally distributed, differences in distributions were examined using the Kruskal-Wallis test.

Generalized linear models were fit to examine pairwise differences in estimated least squares mean expression values by exposure to 0, 5, 20, or 100  $\mu\text{g/mL}$  of talc. We used the Tukey-Kramer adjustment for multiple comparisons, and the regression models were fit using log2 transformed analyte expression values after adding a numeric constant “1” to meet model assumptions while avoiding negative transformed values. *P* values below .05 are statistically significant.

## Results

### Talc Treatment Decreased the Expression of Antioxidant Enzymes SOD and CAT in Normal and EOC Cells

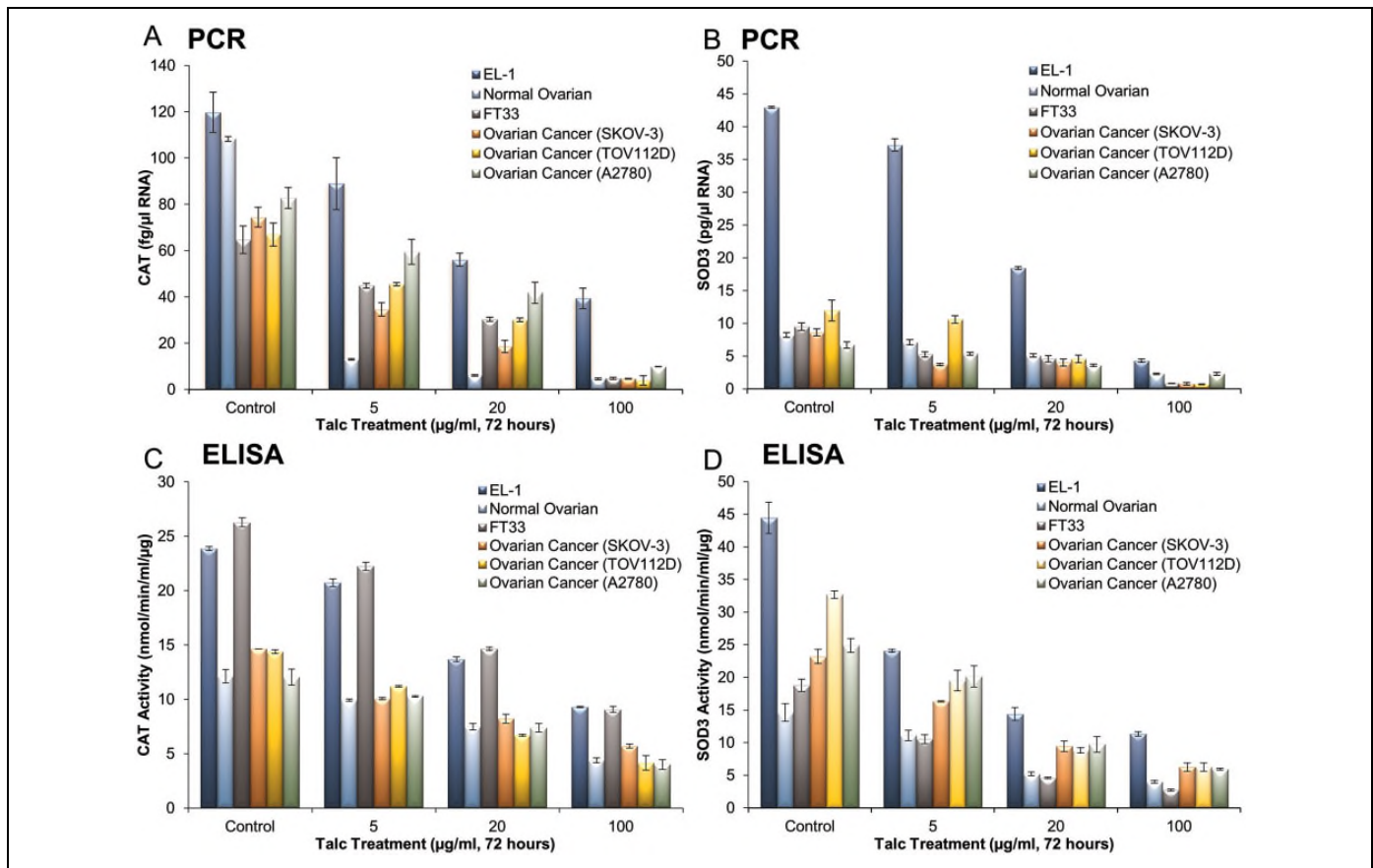
Real-time RT-PCR and ELISA assays were utilized to determine the CAT and SOD messenger RNA (mRNA) and protein levels in cells before and after 72 hours talc treatment, respectively (Figure 1). The CAT (Figure 1A and C) and SOD (Figure 1B and D) mRNA and protein levels were significantly decreased in a dose-dependent manner in talc-treated cells compared to controls ( $P < .05$ ).

### Talc Treatment Increased the Expression of Prooxidants iNOS, $\text{NO}_2^-$ / $\text{NO}_3^-$ , and MPO in Normal and EOC Cells

Real-time RT-PCR and  $\text{NO}_2^-$  / $\text{NO}_3^-$  assays were utilized to determine the iNOS mRNA and NO levels in cells before and after 72 hours talc treatment, respectively (Figure 2). The iNOS mRNA and NO levels were significantly increased in a dose-dependent manner in talc-treated cells as compared to their controls (Figure 2A and C,  $P < .05$ ). As expected, there was no detectable MPO in normal ovarian and fallopian tube cells, and thus, talc treatment did not have any effect. However, MPO mRNA and protein levels were significantly increased in a dose-dependent manner in talc-treated ovarian cancer cells and macrophages compared to controls (Figure 2B and D,  $P < .05$ ).

### Talc Treatment Decreased the Expression of Antioxidant Enzymes, GPX and GSR, in Normal and EOC Cells

Real-time RT-PCR and ELISA assays were utilized to determine the GPX and GSR mRNA and protein levels in cells before and



**Figure 1.** Decreased expression and activity of key antioxidant enzymes, CAT and SOD3. The mRNA (real-time RT-PCR) and protein/activity levels (ELISA) of CAT (A and C) and SOD3 (B and D) were determined in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ( $P < .05$ ) in all cells and in all doses as compared to controls. CAT indicates catalase; SOD3, superoxide dismutase 3; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

after 72 hours of talc treatment, respectively (Figure 3). The GPX (Figure 3A and C) and GSR (Figure 3B and D) mRNA and protein levels were significantly decreased in a dose-dependent manner in talc-treated cells compared to controls ( $P < .05$ ).

#### **Talc Exposure Induced Known Genotype Switches in Key Oxidant and Antioxidant Enzymes**

Talc treatment was associated with a genotype switch in *NOS2* from the common C/C genotype in untreated cells to T/T, the SNP genotype, in talc-treated cells, except in A2780 and TOV112D (Table 2). Additionally, the observed decrease in CAT expression and activity was associated with a genotype switch from common C/C genotype in CAT in untreated cells to C/T, the SNP genotype, in TOV112D and all normal talc-treated cells. However, there was no detectable genotype switch in CAT in A2780, SKOV3, and TOV112D (Table 2). Remarkably, there was no observed genotype switch in the selected SNP for SOD3 and GSR in all talc-treated cells. All cells, except for HOSEpiC cells, manifest the SNP genotype of

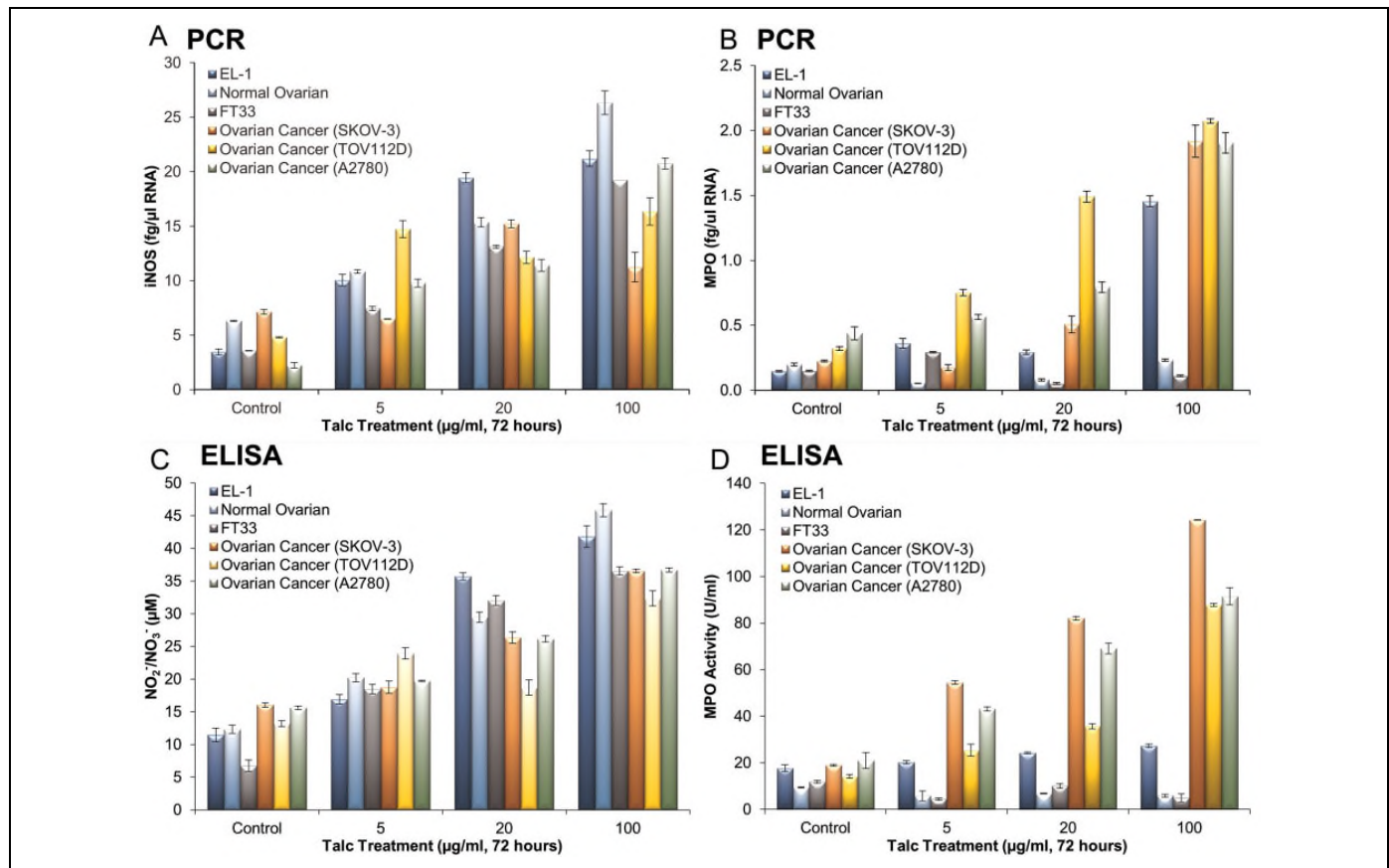
*GPX1* (C/T). Intriguingly, talc treatment reversed this SNP genotype to the normal genotype (Table 2).

#### **Talc Treatment Increased CA-125 Levels in Normal and EOC Cells**

CA-125 ELISA assay was performed in protein isolated from cell media before and after talc treatment. CA-125 levels were significantly increased in a dose-dependent manner in all cells (Figure 4,  $P < .05$ ). There was no detectable CA-125 protein in macrophages.

#### **Talc Treatment Increased Cell Proliferation and Decreased Apoptosis**

MTT cell proliferation assay was used to determine cell viability, and caspase-3 activity assay was utilized to determine apoptosis of all cell lines after 24 hours of talc treatment (Figure 5). Cell proliferation was significantly increased from the baseline in all talc-treated cells ( $P < .05$ ), but to a greater degree in normal



**Figure 2.** Increased expression and activity of key prooxidants, iNOS, NO<sub>2</sub>/NO<sub>3</sub><sup>-</sup>, and MPO. The mRNA (real-time RT-PCR) and protein/activity levels (ELISA) of iNOS (A and C) and MPO (B and D) were determined in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. As expected, there was no detectable MPO in normal ovarian and fallopian tube cells, and thus, talc treatment did not have any effect. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ( $P < .05$ ) in iNOS and MPO-positive cells and in all doses as compared to controls. iNOS indicates inducible nitric oxide synthase; MPO, myeloperoxidase; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

as compared to cancer cells. As anticipated, caspase-3 was significantly reduced in cancer as compared to normal cells. Talc treatment resulted in decreased caspase-3 activity in all cells as compared to controls (Figure 6,  $P < .05$ ), indicating a decrease in apoptosis.

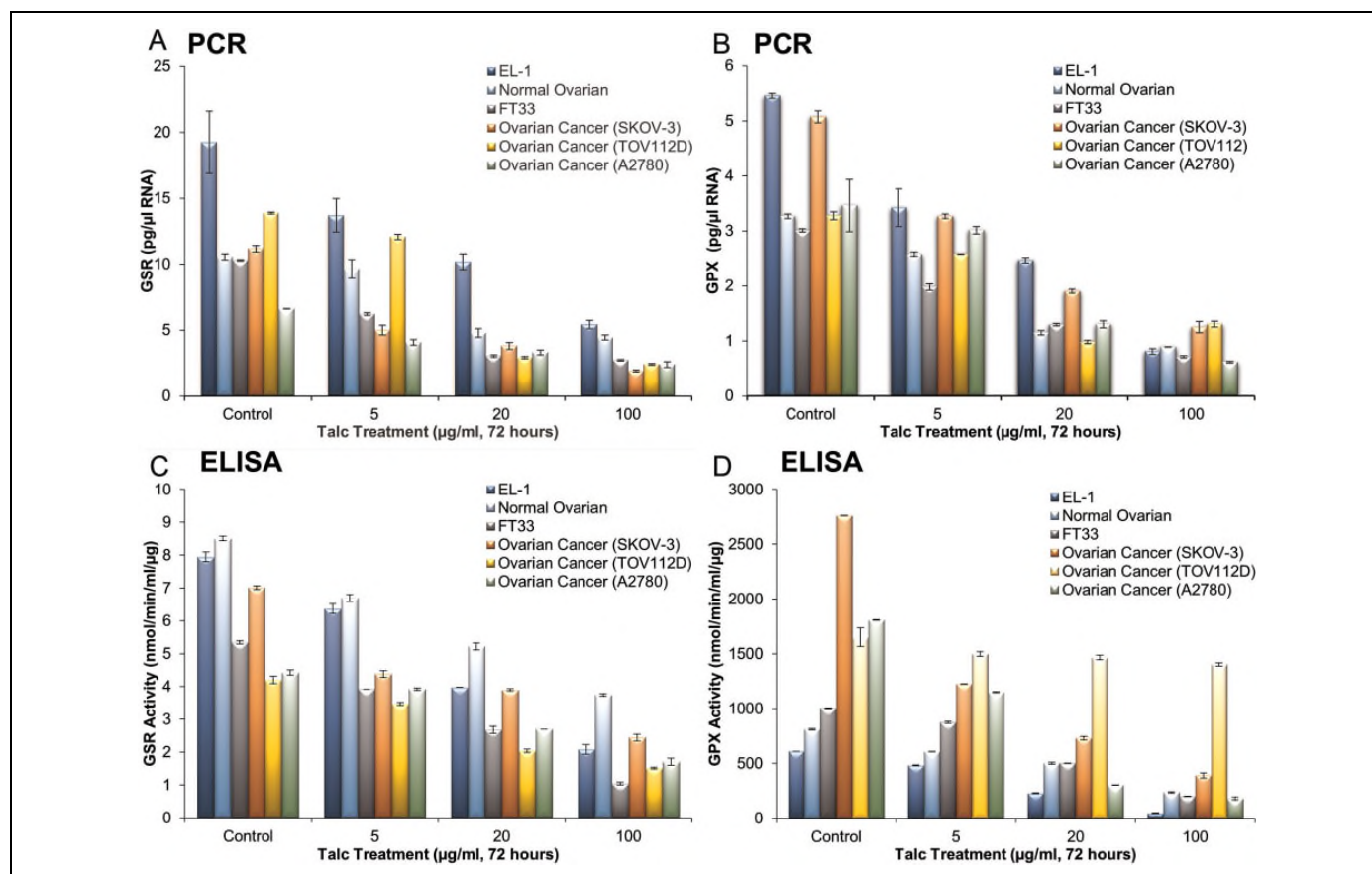
## Discussion

The claim that regular use of talcum powder for hygiene purpose is associated with an increased risk of ovarian cancer is based on several reports confirming the presence of talc particles in the ovaries and other parts of the female reproductive tract as well as in lymphatic vessels and tissues of the pelvis.<sup>7-12</sup> The ability of talc particles to migrate through the genital tract to the distal fallopian tube and ovaries is well accepted.<sup>10</sup> To date, the exact mechanism is not fully understood, though several studies have pointed toward the peristaltic pump feature of the uterus and fallopian tubes, which is known to enhance transport of sperm into the oviduct ipsilateral to the ovary bearing the dominant follicle.<sup>8-12</sup>

There are reports supporting the epidemiologic association of talc use and risk of ovarian cancer.<sup>11,12</sup> Recent studies have shown that risks for EOC from genital talc use vary by histologic subtype, menopausal status at diagnosis, hormone therapy use, weight, and smoking. These observations suggest that estrogen and/or prolactin may play a role via macrophage activity and inflammatory response to talc. There has been debate as to the significance of the epidemiologic studies based on the fact that the reported epidemiologic risk of talc use and risk of ovarian cancer, although consistent, are relatively modest (30%-40%), and there is inconsistent increase in risk with duration of use. This observation is due, in part, to the challenges in quantifying exposure as well as the failure of epidemiological studies to obtain necessary information about the frequency and duration of usage.<sup>11-13</sup>

In this study, we have shown beyond doubt that talc alters key redox and inflammatory markers, enhances cell proliferation, and inhibits apoptosis, which are hallmarks of ovarian cancer. More importantly, this effect is also manifested by talc in normal cells, including surface ovarian epithelium,





**Figure 3.** Decreased expression and activity of key antioxidant enzymes, GSR and GPX. The mRNA (real-time RT-PCR) and protein/activity levels (ELISA) of GSR (A and C) and GPX (B and D) were determined in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ( $P < .05$ ) in all cells and in all doses as compared to controls. GSR indicates glutathione reductase; GPX, glutathione peroxidase; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

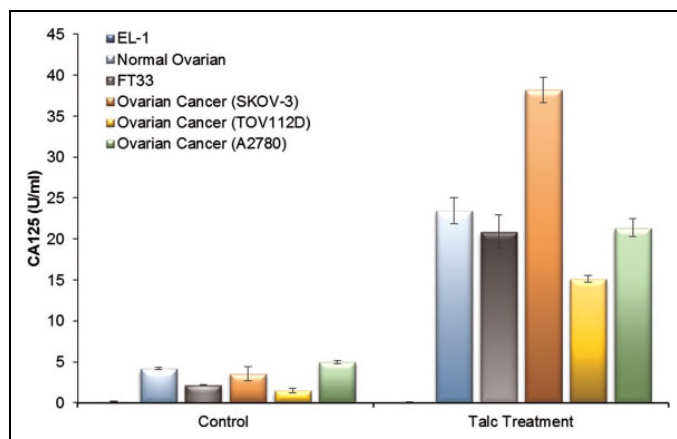
fallopian tube, and macrophages. Oxidative stress has been implicated in the pathogenesis of ovarian cancer, specifically by increased expression of several key prooxidant enzymes such as iNOS, MPO, and NAD(P)H oxidase in EOC tissues and cells as compared to normal cells indicating an enhanced redox state, as we have recently demonstrated (Figure 7).<sup>6</sup> This redox state is further enhanced in chemoresistant EOC cells as evident by a further increase in iNOS and  $\text{NO}_2^-/\text{NO}_3^-$  and a decrease in GSR levels, suggesting a shift toward a prooxidant state.<sup>6</sup> Antioxidant enzymes, key regulators of cellular redox balance, are differentially expressed in various cancers, including ovarian.<sup>6,14</sup> Specifically, GPX expression is reduced in prostate, bladder, kidney, and estrogen receptor negative breast cancer cell lines, though GPX is increased in other cancerous tissues from breast.<sup>14</sup> Glutathione reductase levels, on the other hand, are elevated in lung cancer, although differentially expressed in breast and kidney cancer.<sup>5,15</sup> Similarly, CAT was decreased in breast, bladder, and lung cancer while increased in brain cancer.<sup>16-18</sup> Superoxide dismutase is expressed in lung, colorectal, gastric ovarian, and breast

cancer, while decreased activity and expression have been reported in colorectal carcinomas and pancreatic cancer cells.<sup>18-21</sup> Collectively, this differential expression of antioxidants demonstrates the unique and complex redox microenvironment in cancer. Glutathione reductase is a flavoprotein that catalyzes the NADPH-dependent reduction of oxidized glutathione (GSSG) to GSH. This enzyme is essential for the GSH redox cycle that maintains adequate levels of reduced cellular GSH. A high GSH to GSSG ratio is essential for protection against oxidative stress (Figure 5). Treatment with talc significantly reduced GSR in normal and cancer cells, altering the redox balance (Figure 3A and C). Likewise, GPX is an enzyme that detoxifies reactive electrophilic intermediates and thus plays an important role in protecting cells from cytotoxic and carcinogenic agents. Overexpression of GPX is triggered by exogenous chemical agents and reactive oxygen species and is thus thought to represent an adaptive response to stress.<sup>15</sup> Indeed, treatment of normal and cancer cells with talc significantly reduced GPX, which compromised the overall cell response to stress (Figure 3B and D).

**Table 2.** SNP Characteristics (A) and SNP Genotyping of Key Redox Enzymes in Untreated and Talc-Treated (100 µg/mL) Human Primary Ovarian Epithelial Cells (Normal Ovarian), Human Ovarian Surface Epithelial Cells (HOSEpiC), Fallopian Tube (FT33), and Ovarian Cancer (A2780, SKOV-3, TOV112D) Cell Lines (B).

	Gene (rs Number)				
	CAT (rs769217)	NOS <sub>2</sub> (rs2297518)	GSR (rs8190955)	GPX1 (rs3448)	SOD3 (rs2536512)
<b>A</b>					
MAF	0.123	0.173	0.191	0.176	0.476
SNP	C-262T	C2087T	G201T	C-1040T	A377T
Chromosome location	11p13	17q11.2	8p12	3q21.31	4p15.2
Amino acid switch	Isoleucine to Threonine	Serine to Leucine	Unknown	Unknown	Alanine to threonine
Effect on activity	Decrease	Increase	Unknown	Unknown	Decrease
<b>B</b>					
A2780: Control	C/C	C/C	G/G	C/T	A/A
A2780: Talc	C/C	C/C	G/G	C/C	A/A
SKOV-3: Control	C/C	C/C	G/G	C/T	A/A
SKOV-3: Talc	C/C	T/T	G/G	C/C	A/A
TOV112D: Control	C/C	C/C	G/G	C/T	A/A
TOV112D: Talc	C/T	C/C	G/G	C/C	A/A
HOSEpiC: Control	C/C	C/C	G/G	C/T	A/A
HOSEpiC: Talc	C/T	T/T	G/G	C/T	A/A
FT33: Control	C/C	C/C	G/G	C/T	A/A
FT33: Talc	C/T	T/T	G/G	C/C	A/A
Normal ovarian: Control	C/C	C/C	G/G	C/T	A/A
Normal ovarian: Talc	C/T	T/T	G/G	C/C	A/A

Abbreviation: SNP, single-nucleotide polymorphism.

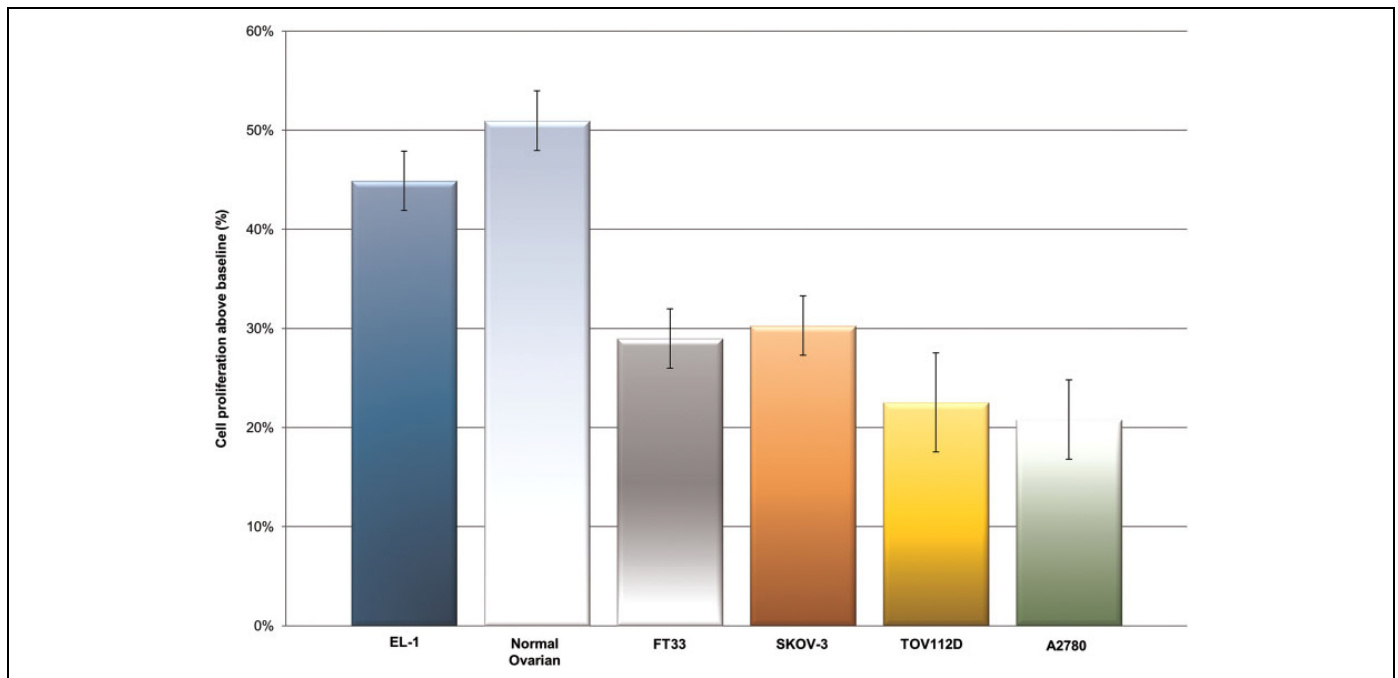
**Figure 4.** Increased CA-125 levels in response to talc treatment. The level of ovarian cancer biomarker CA-125 was determined by ELISA before and after 72 hours of talc treatment (100 µg/mL) in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cells. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ( $P < .05$ ) in all cells as compared to controls. ELISA indicates enzyme-linked immunosorbent assay.

We have previously reported that EOC cells manifest increased cell proliferations and decreased apoptosis.<sup>6</sup> In this study, we have shown that talc enhances cell proliferation and induces an inhibition in apoptosis in EOC cells, but more importantly in normal cells, suggesting talc is a stimulus to the development of the oncogenic phenotype. We also previously

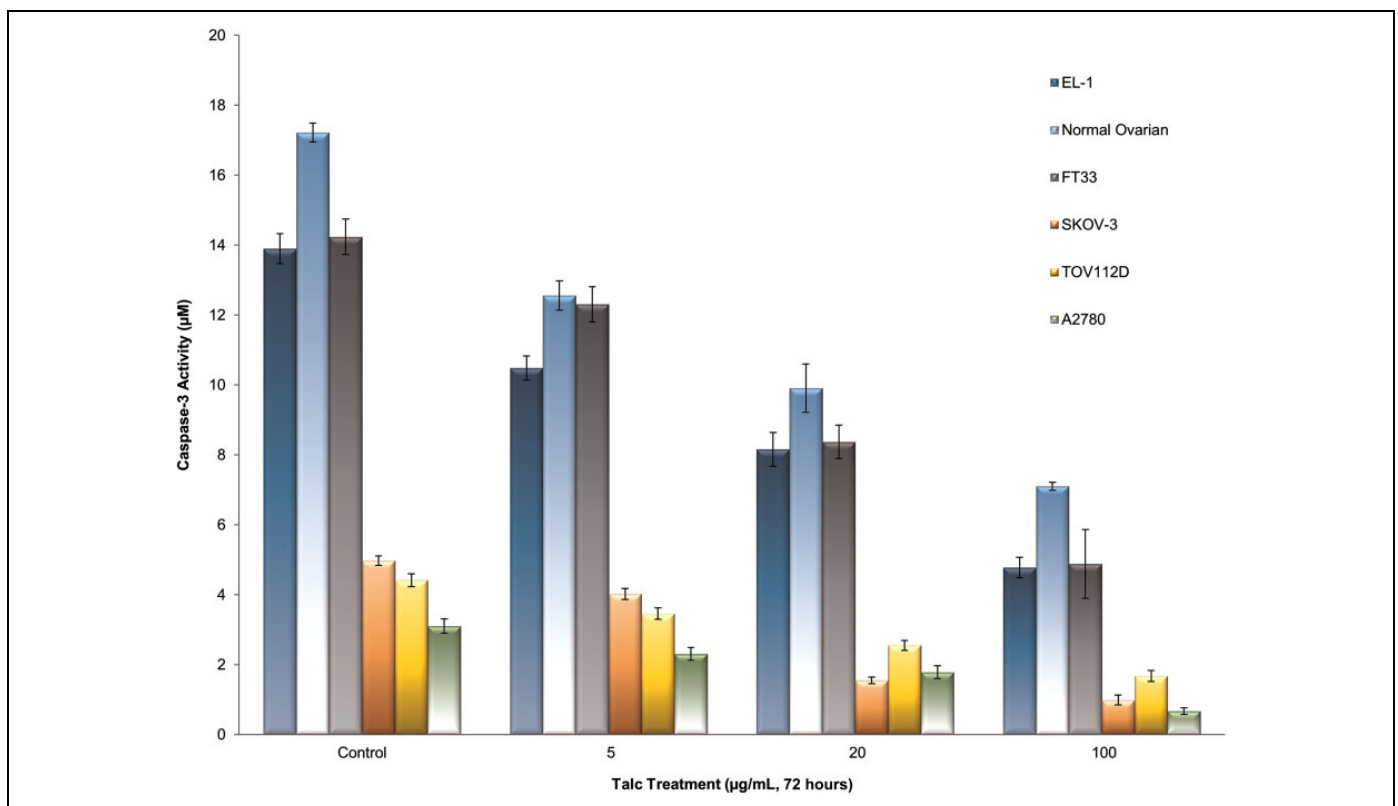
reported a cross talk between iNOS and MPO in ovarian cancer, which contributed to the lower apoptosis observed in ovarian cancer cells.<sup>6,22</sup> Myeloperoxidase, an abundant hemoprotein, previously known to be present solely in neutrophils and monocytes, is a key oxidant enzyme that utilizes NO produced by iNOS as a 1-electron substrate generating NO<sup>+</sup>, a labile nitrosylating species.<sup>6,23,24</sup> We were the first to report that MPO was expressed by EOC cells and tissues and that silencing MPO gene expression utilizing MPO-specific siRNA induced apoptosis in EOC cells through a mechanism that involved the S-nitrosylation of caspase-3 by MPO.<sup>22</sup> Additionally, we have compelling evidence that MPO serves as a source of free iron under oxidative stress, where both NO<sup>+</sup> and superoxide are elevated.<sup>6</sup> Iron reacts with hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and catalyzes the generation of highly reactive hydroxy radical (HO<sup>•</sup>), thereby increasing oxidative stress, which in turn increases free iron concentrations by the Fenton and Haber-Weiss reaction.<sup>6,24</sup> We have previously highlighted the potential benefits of the combination of serum MPO and free iron as biomarkers for early detection and prognosis of ovarian cancer.<sup>25</sup> Collectively, we now have substantial evidence demonstrating that altered oxidative stress may play a role in maintaining the oncogenic phenotype of EOC cells. Treatment of normal or ovarian cancer cells with talc resulted in a significant increase in MPO and iNOS, supporting the role of talc in the enhancement of a prooxidant state that is a major cause in the development and maintenance of the oncogenic phenotype (Figure 2).

Furthermore, CA-125, which exists as a membrane-bound and secreted protein in EOC cells, has been established as a

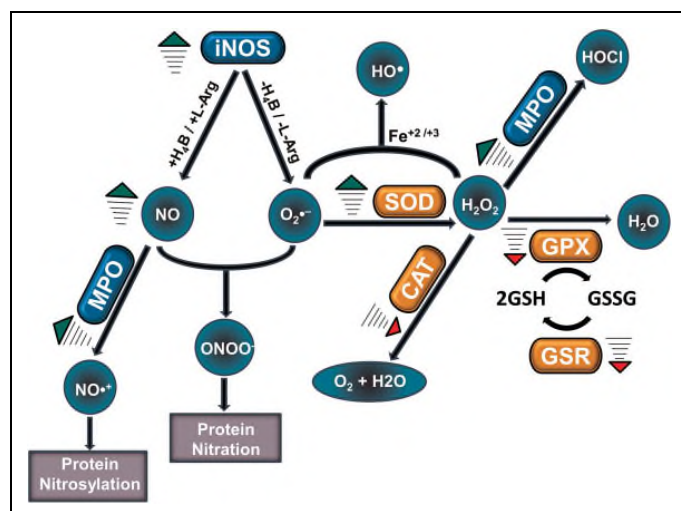




**Figure 5.** Increased cell proliferation in response to talc treatment. Cell proliferation was determined by MTT cell proliferation assay after 24 hours of talc treatment (100 µg/mL) in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cells. Experiments were performed in triplicate. Cell proliferation is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ( $P < .05$ ) in all cells as compared to controls.



**Figure 6.** Decreased apoptosis in response to talc treatment. Caspase-3 activity was used to measure the degree of apoptosis in all cells. Caspase-3 activity assay was utilized to determine caspase-3 activity in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard error. All changes in response to talc treatment were significant ( $P < .05$ ) in all cells and in all doses as compared to controls.



**Figure 7.** Epithelial ovarian cancer (EOC) cells have been reported to manifest a persistent prooxidant state as evident by the upregulation (green arrows) of key oxidants iNOS, NO, NO<sup>+</sup>, ONOO<sup>-</sup>, OH<sup>·</sup>, O<sub>2</sub><sup>·-</sup>, and MPO (blue) and downregulation (red arrows) of key antioxidants SOD, CAT, GPX, and GSR (orange). This redox state was also shown to be further enhanced in chemoresistant EOC cells. In this study, talcum powder altered the redox state, as indicated by the arrows, of both normal and EOC cells to create an enhanced prooxidant state. iNOS indicates inducible nitric oxide synthase; MPO, myeloperoxidase; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; GSR, glutathione reductase.

biomarker for disease progression and response to treatment.<sup>2</sup> CA-125 expression was significantly increased from nearly undetectable levels in controls to values approaching clinical significance (35 U/mL in postmenopausal women<sup>26</sup>) in talc-treated cells (Figure 4,  $P < .05$ ) without the physiologic effects on the tumor microenvironment one would expect to be present in the human body, thus highlighting the implications of the prooxidant states caused by talc alone.

To elucidate the mechanism by which talc alters the redox balance to favor a prooxidant state not only in ovarian cancer cells, but more importantly in normal cells, we have examined selected known gene mutations corresponding to SNPs known to be associated with altered enzymatic activity and increased cancer risk.<sup>6,27</sup> Our results show that the *CAT* SNP (rs769217) resulting in decreased enzymatic activity was induced in all normal cell lines tested and in TOV112D EOC lines, but was not detected in A2780 or SKOV-3 cell lines (Table 2). Nevertheless, our results confirm a decrease in *CAT* expression and enzymatic activity in all talc-treated cells (Figure 1), indicating the existence of other *CAT* SNPs. The *SOD3* (rs2536512) and *GSR* (rs8190955) SNP genotypes were not detected in any cell line, yet *SOD3* and *GSR* activity and expression were decreased in all talc-treated cells, again suggesting the presence of other SNPs. Our results have also shown that all cells, except for HOSEpiC cells, manifest the SNP genotype of *GPX1* (C/T) before talc treatment. Intriguingly, talc treatment reversed this SNP genotype to the normal genotype (Table 2). Consistent with this finding, we have previously reported that acquisition

of chemoresistance by ovarian cancer cells is associated with a switch from the *GPX1* SNP genotype to the normal *GPX1* genotype.<sup>6</sup> It is not understood why a *GPX1* SNP genotype predominates in untreated normal and ovarian cancer cells. Our results showed that talc treatment was associated with a genotype switch from common C/C genotype in *NOS2* in untreated cells to T/T, the SNP genotype, in talc-treated cells, except in A2780 and TOV112D (Table 2). Nevertheless, our results confirm an increase in iNOS expression and enzymatic activity in all talc-treated cells (Figure 2), again suggesting the existence of other *NOS2* SNPs. Collectively, these findings support the notion that talc treatment induced gene point mutations that happen to correspond to SNPs in locations with functional effects, thus altering overall redox balance for the initiation and development of ovarian cancer. Future studies examining such SNPs are important to fully elucidate a genotype switch mechanism induced by talc exposure.

In summary, this is the first study to clearly demonstrate that talc induces inflammation and alters the redox balance favoring a prooxidant state in normal and EOC cells. We have shown a dose-dependent significant increase in key prooxidants, iNOS, NO<sub>2</sub>/NO<sub>3</sub>, and MPO, and a concomitant decrease in key antioxidant enzymes, CAT, SOD, GPX, and GSR, in all talc-treated cells (both normal and ovarian cancer) compared to their controls. Additionally, there was a significant increase in CA-125 levels in all the talc-treated cells compared to their controls, except in macrophages. The mechanism by which talc alters the cellular redox and inflammatory balance involves the induction of specific mutations in key oxidant and antioxidant enzymes that correlate with alterations in their activities. The fact that these mutations happen to correspond to known SNPs of these enzymes indicate a genetic predisposition to developing ovarian cancer with genital talcum powder use.

### Authors' Note

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### Acknowledgment

Special thanks to Imaan Singh for her technical contributions in acquiring the data and in development of graphics.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Saed has served as a paid consultant and expert witness in the talcum powder litigation.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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